JACC Vol. 27, No. 1
January 1996:218–24

Transvenous Procurement of Pulmonary Artery Smooth Muscle and Endothelial Cells Using a Novel Endoarterial Biopsy Catheter in a Canine Model

ABRAHAM ROTHMAN, MD, FACC, DAVID M. MANN,* MARK T. HOUSE,* RON G. KONOPKA, PETER G. CHILES, CRAIG A. PEDERSEN, PAUL WOLF, MD, KENNETH M. MOSER, MD

San Diego, California

Objectives. **The aim of this study was to evaluate the performance of a new arterial biopsy catheter in obtaining pulmonary endovascular samples in a canine model.**

Background. **Percutaneous endomyocardial biopsy is a widely used and valuable procedure in the management of posttransplant rejection and selected cardiomyopathies. A similar method of obtaining endoarterial biopsy samples would aid in the study, diagnosis and management of arterial diseases.**

Methods. **Catheterization was performed in 19 dogs, each weighing 20 to 30 kg, through an 8F sheath in the external jugular vein to obtain pulmonary endoarterial samples. The catheter consists of two sliding tubes: an inner one with a beveled opening that accommodates endoarterial tissue by means of a vacuum and an outer tube with a sharp distal edge that cuts the tissue when activated.**

Results. **Overall, a total of 266 separate biopsy attempts were performed, and 161 tissue samples were obtained (success rate 61%). With modifications in technique in the last nine dogs, 54 (93%) of 58 attempts were successful. There were no deaths, extravasation of contrast material on angiography or thrombi. Of 20 vessels with prebiopsy and postbiopsy angiograms, 1 developed transient spasm (5%). On microscopic examination of cross sections of 50 separate pulmonary endoarterial biopsy samples, all had smooth muscle cells and 30 contained endothelial cells (60%). The arteries of origin showed small intimal and medial tears and mild perivascular hemorrhage. Angiographic and pathologic examination of previously biopsied arterial segments 2 weeks (two dogs) and 8 weeks (two dogs) after the procedure showed patent vessels and no thrombi. Histologically, the biopsy sites revealed mild neointimal and medial proliferation.**

Conclusions. **This new endoarterial biopsy catheter is safe and effective in obtaining pulmonary artery samples in normotensive dogs.**

(J Am Coll Cardiol 1996;27:218–24)

In 1962, Sakakibara and Konno (1) reported the development of the bioptome catheter and a technique for intracardiac biopsy. Since then, transvenous endomyocardial biopsy has become a widespread and valuable procedure for the detection and grading of cardiac transplant rejection, diagnosis of myocarditis, determination of doxorubicin cardiotoxicity and diagnosis of specific infiltrative diseases, such as sarcoidosis, amyloidosis and glycogen storage disease (2). A similar percutaneous method of obtaining arterial wall biopsy samples has not been described. Such a technique would facilitate the study, diagnosis, development of new treatment strategies and monitoring of the evolution of arterial diseases. We describe a new biopsy catheter designed to obtain endoarterial samples and evaluate its performance in distal pulmonary arteries of normotensive dogs.

Methods

Study protocol. This study protocol was approved by the Animal Subjects Committee of the University of California San Diego, and the procedures followed were in accordance with institutional guidelines. Nineteen mongrel dogs weighing 20 to 30 kg received 10 mg/kg body weight of intravenous propofol, underwent intubation and ventilation at a rate of 12 breaths/min and were maintained under anesthesia with 1.5% halothane. A femoral artery line was placed for monitoring. An 8F sheath was placed percutaneously in the external jugular vein, and a 7F endhole catheter (Arrow, Inc.) was advanced through this sheath to a distal lower lobe pulmonary artery, where pressures were recorded. An 0.038-in. (0.095 cm), 260-cm extrastiff Amplatz exchange guide wire (Meditech, Inc.) was passed through the end-hole catheter. The end-hole catheter was exchanged for an 8F Blue Mullins Introducer sheath (75 cm long) (Cook, Inc.) that was adapted with a radiopaque band at the distal end and shaped with a heat gun to conform to the right cardiopulmonary pathway.

From the Division of Pediatric Cardiology, Department of Pediatrics, Division of Pulmonary and Critical Care Medicine, Department of Medicine and Department of Pathology, University of California San Diego; and *Vascular BioSciences Co., San Diego, California.

Manuscript received April 20, 1995; revised manuscript received July 7, 1995, accepted August 10, 1995.

Address for correspondence: Dr. Abraham Rothman, University of California San Diego Medical Center, 8445, 200 West Arbor Drive, San Diego, California 92103.

©1996 by the American College of Cardiology

0735-1097/96/$15.00
0735-1097(95)00422-X

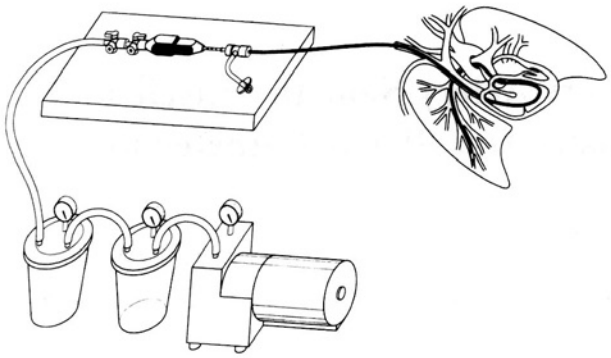


Figure 1. Endoarterial biopsy catheter procedural configuration. The biopsy catheter is connected externally to a vacuum source consisting of two suction cannisters in series with a vacuum pump. The endoarterial biopsy catheter is directed to a desired sampling site through a long 8F sheath, which is placed by percutaneous technique and advanced through the right heart into a distal pulmonary artery branch.

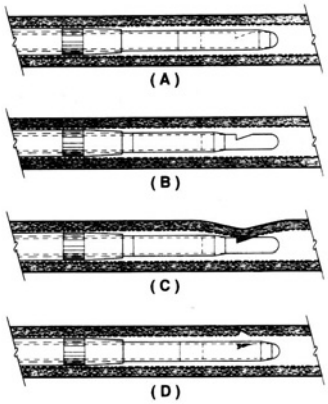


Figure 2. Schematic representation of the biopsy sampling procedure. The distal end of the catheter is shown extending from the distal end of the radiopaque-tipped introducer sheath, with the outer tube covering the beveled opening of the inner tube (**A**). The outer tube is retracted, exposing the inner tube (**B**). On vacuum transmission through the inner tube, an endoarterial tissue sample is drawn into the beveled opening (**C**). The outer tube is advanced over the inner tube, severing the tissue sample (**D**).

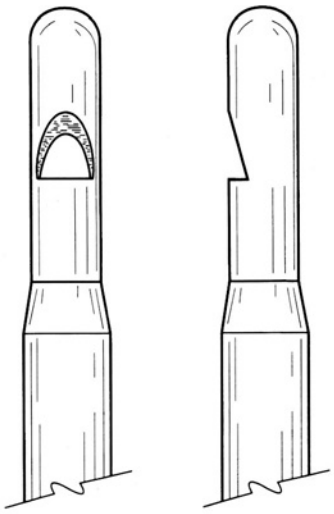
Each dog was given 100 U/kg of heparin. A 7F Berman angiographic catheter (Arrow, Inc.) was advanced through the sheath into a 2.5- to 3.0-mm distal pulmonary artery branch, where an angiogram was obtained. The angiographic catheter served as a guide to advance the stiff sheath into a small vessel targeted for biopsy and was then exchanged for the endoarterial biopsy catheter (Fig. 1). In the first four dogs, we also performed endoarterial biopsies of the left carotid artery under direct vision.

Endoarterial biopsy catheter. The catheter has an external diameter of 2.5 mm (7.9F) and is composed of two flexible polymeric tubes that slide relative to each other. The inner tube has a stainless steel distal end with a beveled opening that is designed to accommodate arterial tissue. A vacuum is coupled to the inner tube and channeled to the beveled opening. The outer tube terminates in a stainless steel cutting tube. The proximal ends of the two tubes are fitted with handles. To obtain the biopsy sample, a vacuum is transmitted to the beveled opening of the inner tube, causing a tissue sample to be drawn in. The outer tube is then advanced over the inner tube, severing the tissue sample (Fig. 2). The beveled opening is formed by the intersection of a proximal end surface that is perpendicular to the long axis of the catheter tip and a distal beveled surface situated at an angle to the catheter tip (Fig. 3). With this design, the area of artery contacted by the outer periphery of the beveled opening is larger than the inner aperture connected to the vacuum, thus maintaining the tissue sample with its orientation preserved.

A variety of beveled window sizes were tested for their ability to transmit the vacuum and preserve the tissue samples. If the size of the beveled opening was <1.0 mm in the axis parallel to the long axis of the catheter, vacuum transmission was inadequate for biopsy sampling. Therefore, subsequent catheters were manufactured with a beveled opening long axis dimension >1.0 mm.

The amount of vacuum required to draw in pulmonary artery tissue samples and allow cutting by the outer tube is determined by the ultimate vacuum of the vacuum source, the narrowest opening in the vacuum transmittance pathway and the vacuum differential between the open and closed configurations of the beveled window. In our study, the source of the vacuum was a two-stage rotary vane vacuum pump (Dayton Electrical Mfg. Co.) that could achieve an ultimate vacuum of 29.9 in. Hg. To obtain pulmonary endoarterial samples reliably in these normal dogs, a differential of at least 2 in. Hg in vacuum (open versus closed beveled window) was required. If the internal diameter of the inner catheter tube was <1.0 mm, this difference in vacuum could not be attained. Subsequent

Figure 3. Configuration of the distal catheter. Top (**left**) and side (**right**) views of the beveled opening in the distal metal tip of the inner catheter tube.



JACC Vol. 27, No. 1
January 1996:218–24

catheters were made with an inner tube internal dimension of 1.3 mm. These catheters could pull ~26.5 in. Hg of vacuum with the beveled window open and 29.0 in. Hg of vacuum with the beveled window closed, giving a vacuum differential of 2.5 in. Hg.

Procedure. To perform the biopsy procedure, the stiff sheath was wedged into a small distal pulmonary artery branch, and multiple biopsy samples were obtained. After each biopsy, the catheter was removed and the tissue specimen placed in either formalin for histologic examination or appropriate culture media. To stimulate smooth muscle cell growth, samples were placed in media 199 (Gibco) + 20% fetal calf serum, 2 mmol/liter L-glutamine, penicillin and streptomicin. To stimulate endothelial cell growth, separate samples were placed in endothelial cell basal and growth media (Clonetics).

After the biopsy procedures were completed, repeat angiograms were obtained to assess the degree of vascular injury, including the presence of thrombus, vascular occlusion, extravasation of contrast material or aneurysm formation.

Acute study. In the acute experiments, 13 dogs were euthanized immediately after the biopsy procedure. The lungs were examined grossly from the external surface, and the pulmonary arteries were then dissected and examined with specific attention to the sites of sheath manipulation and biopsy. The biopsied arterial segments were excised and placed in formalin for histologic examination.

Chronic study. In the chronic experiments, six dogs were allowed to recover after the biopsy procedure. Two dogs at 2 weeks and two dogs at 8 weeks underwent repeat angiography, followed by euthanasia and histologic examination as previously described. Two dogs are doing well clinically and are still under study 6 months after the biopsy procedure.

Results

Success rate. The 19 dogs underwent a total of 266 separate biopsy attempts. Of these, 161 yielded pulmonary endoarterial samples (success rate 61%). After the experiments in the first four animals, the technique was modified, leading to improved sample retrieval rates: 124 (70%) of 177 biopsy attempts in the next 15 dogs and 54 (93%) of 58 biopsy attempts in the last 9 dogs.

Effects of biopsy procedure. Introduction of the stiff guide wire and stiff sheath through the right heart caused small or no changes in systemic blood pressure and occasional premature ventricular beats. Once the sheath was in good position, passage of the biopsy catheter, sampling of the artery and removal of the biopsy catheter (leaving the sheath in place) did not cause changes in systemic blood pressure or cardiac rhythm.

All dogs in these experiments had normal pulmonary artery pressure (<25 mm Hg systolic). The prebiopsy angiograms of distal right (Fig. 4) or left lower lobe branches showed smooth vessels with uniform branching, a normal capillary cycle time and brisk venous return to the left atrium. Twenty separate arteries had adequate prebiopsy and postbiopsy angiographic results for analysis. Of these, one vessel (5%) on the postbiopsy angiogram was initially occluded but opened toward the end of the contrast injection, suggesting the presence of transient spasm. Another seven arteries developed irregular vessel wall contours on postbiopsy angiography but retained brisk flow. The other 12 vessels maintained intact appearance and flow on postbiopsy angiography. No instances of contrast extravasation into pulmonary parenchymal tissue were observed, even in one dog that underwent 11 consecutive biopsies in the same distal pulmonary artery branch.

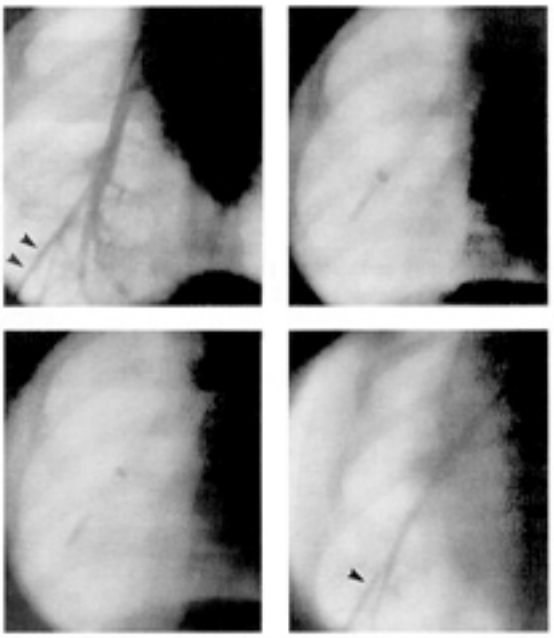


Figure 4. Pulmonary artery angiograms before and after the biopsy procedure. Distal right lower lobe branch pulmonary artery angiogram before biopsy depicting the target sampling site (**arrowheads, top left**). A radiopaque marker denotes the distal end of the guiding sheath through which the catheter is deployed in the open position (**top right**). At biopsy, the catheter is in the closed position (**bottom left**). Immediately after biopsy, the sampled artery is patent (**arrowhead**), without evidence of contrast extravasation (**bottom right**).

Because the vacuum is connected to two reservoirs in series, we could quantitate the amount of blood that returned when the vacuum was applied. In the first four dogs, the guiding sheath was not wedged into the artery that was being biopsied, and there was a large amount of blood loss into the vacuum traps. With wedging of the sheath during the biopsy in each of the last 15 experiments, there was <10 ml of blood in the proximal trap at the end of the biopsy procedure.

Pathologic examination. Surgically exposed carotid arteries were examined during biopsy attempts under direct vision. If the size of the beveled opening was <1.6 mm, on vacuum application a small external dimple formed in the artery at the site of the window. With larger hole sizes, there was complete invagination of the artery into the beveled opening. Regardless of the size of the beveled opening (maximum 2.2 mm), we did not observe a breech in the outer layer of the artery after biopsy, even after 12 attempts at the same site.

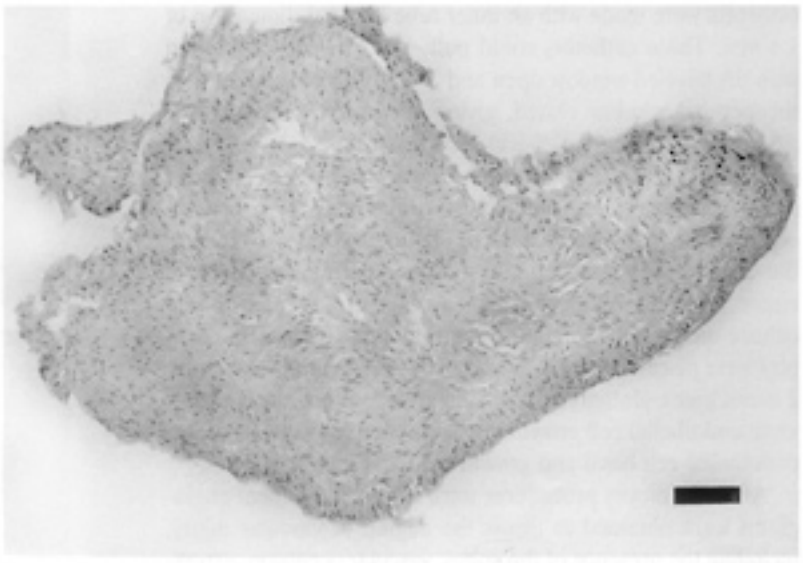


Figure 5. Pulmonary endoarterial biopsy sample. Hematoxylin and eosin staining ×100. **Bar** = 100 μm.

In the dogs that underwent pulmonary artery biopsy, gross examination of the surface regions of the lungs from which biopsy samples were obtained did not reveal evidence of external injury. Postmortem dissection of the pulmonary artery tree, from the main pulmonary artery to the small peripheral arteries in all lobes, revealed absence of thrombi in the vessels that were biopsied and in the neighboring pulmonary arteries.

Fifty biopsy samples were subjected to microscopic examination. All were composed predominantly of smooth muscle cells (Fig. 5); 30 contained endothelial cells (60%) (Fig. 6), and one had a thin layer of adventitia. At the sites of arterial biopsy, tears in the intima and part or all of the media were observed (Fig. 7). In rare samples, the tear extended to the inner layers of the adventitia. Perivascular bleeding was seen frequently on acute histologic examination but was negligible or limited in size in arteries that had undergone fewer than four biopsies and more extensive in arteries that had undergone multiple biopsy samplings.

Cell culture. Smooth muscle cells grew quickly in 24 of 24 attempts, were easily passaged and stained uniformly with anti–smooth muscle myosin antibodies. In the endothelial growth media, endothelial cells were identified in 4 of 27 attempts. Primary cultures were composed of a mixture of endothelial cell islands and fibroblasts. However, after the first subculture, the endothelial cells were outcompeted and overgrown by the fibroblasts.

Chronic study. In the chronic study, the six dogs recovered from the biopsy procedure and anesthesia without complication. None of the animals developed a cough, tachypnea or respiratory distress immediately after the biopsy or during the follow-up period. Two dogs are doing well clinically 6 months after the biopsy procedure.

Follow-up angiography was performed 2 weeks (two dogs) or 8 weeks (four dogs) after biopsy. There was no evidence of thrombus, vascular occlusion or aneurysm formation. Six vessels had good quality postbiopsy and follow-up angiograms for comparison. Three had irregular vascular wall contours at the biopsy site, and three had visually normal vessel walls immediately after the procedure. All six arteries had smooth vascular contours at follow-up angiography 2 weeks (two vessels) or 2 months (four vessels) after biopsy.

In the four dogs that were euthanized, the arterial biopsy sites were difficult to identify by gross pathologic examination because uniform healing had occurred. Histologically, the arterial sites that had been previously biopsied showed mild neointimal proliferation and no perivascular hemorrhage (Fig. 8).

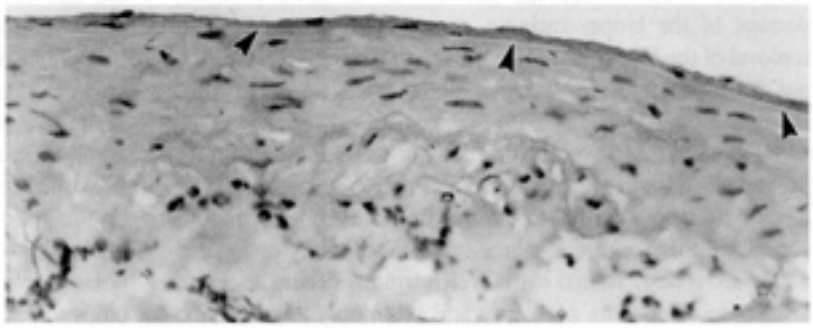


Figure 6. Enlarged view of biopsy sample. A layer of endothelial cells is shown on the lumen surface of the internal elastic lamina (**arrowheads**). Hematoxylin and eosin staining ×200, reduced by 35%.

JACC Vol. 27, No. 1
January 1996:218–24

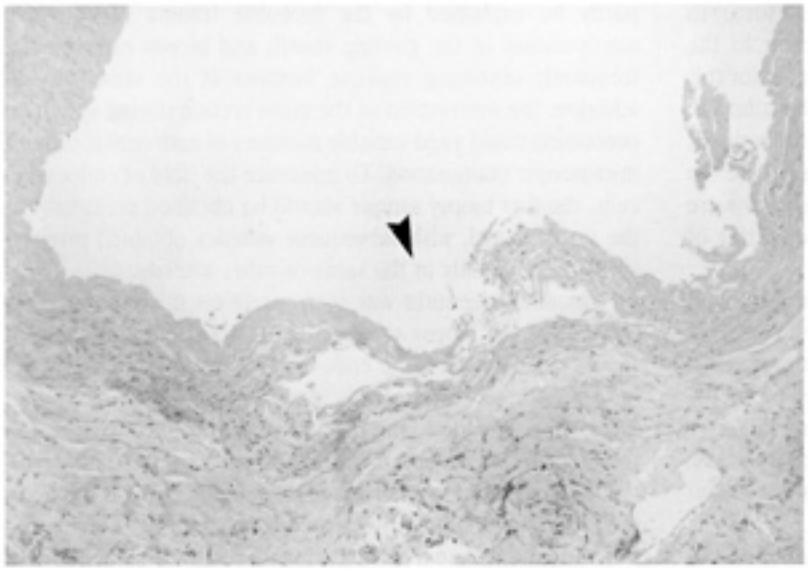


Figure 7. Pulmonary artery site immediately after biopsy procedure. The vascular wall disruption (**arrowhead**) extends through part of the media, but the adventitia is intact. Hematoxylin and eosin staining ×100, reduced by 35%.

Discussion

Pulmonary hypertension is an inexorably progressive disease with imperfect therapeutic options and a high mortality rate (3,4). Other diseases that affect the arterial system, including systemic hypertension (5), polyarteritis nodosa, Wegener's granulomatosis, necrotizing vasculitis (6–8), Takayasu's arteritis (9), Kawasaki disease (10), vascular neoplasms (11), transplantation arteriopathy (12) and Williams syndrome (13) may also cause significant morbidity and mortality, yet their etiology, pathophysiologic mechanism and optimal therapy are still unclear.

Progress in the understanding, diagnosis and management of arterial diseases has been limited in part by the inaccessibility of tissue for examination and experimentation. Percutaneous removal of smooth muscle cells from coronary and peripheral vascular lesions has been reported (14–18) using a directional atherectomy catheter. However, with this method the yield of smooth muscle cells has frequently been insufficient for further studies (14,16), and the mechanism of sample procurement is best suited to obtain material from arteries with atheromatous lesions protruding into the vascular lumen rather than arteries with smooth internal surfaces. Because we have a special interest in the study of pulmonary vascular disease, our aim in this project was to evaluate the efficacy and safety of a new endoarterial biopsy catheter in obtaining tissue samples from peripheral pulmonary arteries. However, minor modifications in the technique should make the procedure applicable to systemic arteries. By procuring endoarterial samples, this method should also be particularly useful in assessing the results of direct drug delivery to the vessel wall (19–21), gene therapy for cardiovascular diseases (22–27) and seeding of the vasculature with cells that have been previously removed from arteries and genetically modified in vitro (28,29).

Catheter design. In contrast to obtaining an endomyocardial biopsy, where the tissue to be sampled is generally perpendicular to the biopsy catheter, for an endoarterial biopsy the tissue to be sampled is generally in parallel with the

Figure 8. Pulmonary artery sampling site 2 months after biopsy procedure. The sampling site shows mild localized neointimal hyperplasia (**large arrowhead**) compared with the normal adjacent artery wall (**small arrowheads**). Hematoxylin and eosin staining ×100, reduced by 35%.

catheter. The difficulty in generating mechanical force to obtain vascular wall samples in a radial orientation to the catheter made the use of a vacuum particularly suitable for this purpose. Hence, the inner tube of the catheter became the dedicated conduit for the vacuum. In addition, the catheter was primarily made of flexible polymeric tubes to negotiate the pathways of the cardiovascular system. Rigid distal ends were attached to both inner and outer tubes to facilitate cutting of the endovascular tissue.

Technique. We found it easier to advance the large and stiff sheath through the right heart of the dogs from an external jugular venous approach rather than from the femoral veins. The use of an 0.038-in. extrastiff guide wire followed by a long, stiff 8F sheath facilitated placement of the biopsy catheter through the right heart to distal right or left pulmonary artery branches. Maintenance of the sheath in the target vessel expedited the repeated sampling attempts.

During preliminary attempts to obtain biopsy samples, the endoarterial biopsy catheter was placed in relatively large pulmonary vessels. On application of the vacuum, there was an unpredictable amount of blood loss, depending on the degree of tissue lodging on the beveled window. To minimize the amount of blood loss and ensure better suctioning of endoarterial tissue into the beveled window, we modified the technique to wedge the guiding sheath during biopsy attempts in distal pulmonary arteries. In this position, when the vacuum was applied, there was no significant return of blood through the inner catheter tube, and the success rate of the procedure increased (93% in the last nine dogs). However, with this method there were instances where the sheath remained wedged between biopsy attempts and air became trapped in the sheath on removal of the biopsy catheter. Attempts to pull back the sheath to remove the air sometimes resulted in sheath kinking. To minimize this problem, the technique was refined to partially wedge the sheath initially, advance the sheath just before biopsy and retract the sheath immediately after sampling but before biopsy catheter removal.

Passage of the biopsy catheter through the curved stiff sheath in the right heart was facilitated by keeping the catheter in the closed position (shortening the total metal tip length at the distal end of the catheter). The addition of a radiopaque marker to the end of the sheath aided in guiding the sheath to the desired position in the vasculature. This change helped optimize success of the biopsy procedure and minimize sheath-related complications in small distal pulmonary arteries. To reduce the possibility of small endoarterial biopsy samples from being suctioned into the vacuum trap, the vacuum was turned off immediately after the outer cutting tube was advanced over the inner tube.

Biopsy samples. Biopsy studies were performed in normotensive dogs. The thickness of the pulmonary artery wall in the vicinity of the biopsy sites was very thin. Therefore, some of the samples that were obtained were also thin and elongated. We speculate that larger pieces will be retrieved from thickened and chronically hypertensive arterial walls.

The paucity of endothelial cells in some biopsy samples can partly be explained by the probable trauma of excessive manipulation of the guiding sheath and biopsy catheter and frequently obtaining multiple biopsies at the same site. In addition, the orientation of the cross section during specimen processing could yield variable numbers of endothelial cells on microscopic examination. To maximize the yield of endothelial cells, the first biopsy sample should be obtained proximally in the target vessel, with subsequent samples obtained progressively more distally in the same or other arteries.

Vascular adventitia was seen rarely on microscopic cross sections of the biopsy samples. On histologic examination of the biopsied arteries, the endovascular tissue removed by the biopsy catheter infrequently extended into the adventitial layer, probably due to the high content of connective tissue in the adventitia, which provides a rigid and resistant layer. Additionally, cutting in an axis parallel to the vessel is relatively ineffective compared with perpendicular cutting. Our procedure also uses manual cutting, which is relatively slow, allowing the vessel time to recoil. Perhaps because of a combination of these factors, the adventitial layer was not breeched in any of the biopsy attempts, even when the vessel was entirely invaginated in the beveled window during carotid artery attempts under direct vision.

Complications. There were no significant complications related to the biopsy procedure. No animal died as a result of the procedure. Changes in blood pressure or cardiac rhythm were minimal and transient during manipulations of the stiff sheath and during the actual biopsy sampling. The amount of blood loss as a result of the vacuum was negligible when the guiding sheath was properly wedged. Angiography performed immediately after vessels were biopsied revealed no thrombi, aneurysms or extravasation. One vessel was completely obstructed at the beginning of the contrast injection but abruptly reestablished flow toward the end of the selective arterial injection. We presume that this was a transient spasm because no thrombus was found at autopsy 1 h later. One-third of the vessels that were biopsied showed an irregular vascular contour on postbiopsy angiography that was probably due to a combination of partial vessel spasm and intimal flaps and tears.

Gross pathologic examination of the pulmonary lobe subjected to biopsy revealed no surface evidence of injury. On microscopic examination of arteries obtained immediately after biopsy, there was a small accumulation of periarterial blood that seemed to increase with the number of biopsy attempts at a single site. The source of blood could be secondary to tracking along disruptions of the endovascular wall or perhaps due to rupture of the vasa vasorum.

Angiography of six arteries 2 to 8 weeks after biopsy demonstrated patent vessels with smooth vascular contours, including three arteries that had irregular lumen borders immediately after biopsy. Gross examination of the arterial biopsy sites revealed no identifiable areas of injury. Microscopically, the perivascular bleeding had resolved, and there were occasional regions of mild neointimal hyperplasia that were presumed to correspond to the previous biopsy sites. Therefore, the biopsied pulmonary vessels in these dogs demon-

strated a prompt and complete healing response within 2 months of the biopsy procedure.

Limitations of the study. The present study has several limitations. The success and safety of the endoarterial biopsy catheter at normal pulmonary artery pressures does not ensure similar results at high pressures. Diminished elasticity of thickened and diseased vessels may limit the ability of the vacuum to pull tissue into the beveled window. Also, vascular disruptions after biopsy may be more prone to extravasation of blood at higher pressures. Other limitations include the size of arteries that can be biopsied with a specific sheath size. The 8F long sheath and 7.9F biopsy catheter that were used in this study are too large to use in small animals or infants. An additional limitation is that the canine pulmonary artery endothelial cells in culture appear to grow with difficulty and are quickly outcompeted by fibroblasts. However, modifications in the catheter, technique and laboratory methods should be able to overcome the majority of these limitations.

Conclusions. The present study describes a new biopsy catheter that appears to be effective and safe in procuring endoarterial samples from distal pulmonary arteries of normotensive dogs. With minor modifications in technique, this catheter should be suitable for sampling of hypertensive pulmonary arteries as well as systemic arteries. Potential future uses include its application as a diagnostic and research tool for inflammatory, genetic, atherosclerotic and idiopathic vascular diseases; posttransplantation arteriopathy; and the evaluation of localized drug delivery and gene therapy for cardiovascular diseases.

References

1. Sakakibara S, Konno S. Endomyocardial biopsy. Jpn Heart J 1962;3:537–43.
2. Waller BF, Slack JD, Orr CM, Adlam JH, Fry E. Endomyocardial biopsy for evaluation, diagnosis and treatment of heart disease. ACC Curr J Rev 1994;3(1):16–9.
3. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results of a national prospective registry. Ann Intern Med 1991;115:343–9.
4. Hayden AM, Robert RC, Kriett JM, Smith CM, Nicholson K, Jamieson SW. Primary diagnosis predicts prognosis of lung transplant candidates. Transplantation 1993;55:1048–50.
5. Oparil S. Arterial hypertension. In: Wyngaarden JB, Smith LH Jr, Bennet JC, editors. Cecil Textbook of Medicine. 19th ed. Philadelphia: Saunders, 1992:253.
6. Glynn MJ. Giant cell arteritis and the necrotizing angiitides. In: Horwitz O, McCombs PR, Roberts B, editors. Diseases of Blood Vessels. Philadelphia: Lea & Febiger;1985:253–62.
7. Ledford DK. Immunologic aspects of cardiovascular disease. JAMA 1992; 268:2923–9.
8. Case records of the Massachusetts General Hospital (case 42-1992). N Engl J Med 1992;327:1226–33.
9. Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's arteriopathy. J Am Coll Cardiol 1988;12:964–72.
10. Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. Circulation 1993;87:1776–80.
11. Baker PB, Goodwin RA. Pulmonary artery sarcomas: a review and report of a case. Arch Pathol Lab Med 1985;109:35–9.
12. Mihatsch MJ, Zollinger HU, Gudat F, et al. Transplantation arteriopathy. Path Microbiol 1975;43:219–23.
13. Rein AJJT, Preminger TJ, Perry SB, Lock JE, Sanders SP. Generalized arteriopathy in Williams syndrome: an intravascular ultrasound study. J Am Coll Cardiol 1993;21:1727–30.
14. Bauriedel G, Windstetter U, DeMaio SJ Jr, Kandolf R, Hofling B. Migratory activity of human smooth muscle cells cultivated from coronary and peripheral primary and restenotic lesions removed by percutaneous atherectomy. Circulation 1992;85:554–64.
15. Leclerc G, Isner JM, Kearney M, et al. Evidence implicating nonmuscle myosin in restenosis: use of in situ hybridization to analyze human vascular lesions obtained by directional atherectomy. Circulation 1992;85:543–53.
16. Dartsch PC, Voisard R, Bauriedel G, Hofling B, Betz E. Growth characteristics and cytoskeletal organization of cultured smooth muscle cells from human primary stenosing and restenosing lesions. Arteriosclerosis 1990;10: 62–75.
17. Pickering JG, Weir L, Rosenfield K, Stetz J, Jekanowski J, Isner JM. Smooth muscle cell outgrowth from human atherosclerotic plaque: implications for the assessment of lesion biology. J Am Coll Cardiol 1992;20:1430–9.
18. MacCleod DC, Strauss BH, DeJong M, et al. Proliferation and extracellular matrix synthesis of smooth muscle cells cultured from human coronary atherosclerotic and restenotic lesions. J Am Coll Cardiol 1994;23:59–65.
19. Azrin MA, Mitchel JF, Fram DB, et al. Decreased platelet deposition and smooth muscle cell proliferation after intramural heparin delivery with hydrogel-coated balloons. Circulation 1994;90:433–41.
20. Fernandez-Ortiz A, Meyer BJ, Mailhac A, et al. A new approach for local intravascular drug delivery: iontophoretic balloon. Circulation 1994;89: 1518–22.
21. Lambert TL, Dev V, Rechavia E, Forrester JS, Litvak F, Eigler NL. Localized arterial wall drug delivery from a polymer-coated removable metallic stent: kinetics, distribution, and bioactivity of forskolin. Circulation 1994;90:1003–11.
22. Nabel EG, Plautz G, Nabel GJ. Site-specific gene expression in vivo by direct gene transfer into the arterial wall. Science 1990;249:1285–8.
23. Steg PG, Feldman LJ, Scoazec JY, et al. Arterial gene transfer to rabbit endothelial and smooth muscle cells using percutaneous delivery of an adenoviral vector. Circulation 1994;90:1648–56.
24. French BA, Mazur W, Ali NM, et al. Percutaneous transluminal in vivo gene transfer by recombinant adenovirus in normal porcine coronary arteries, atherosclerotic arteries and two models of coronary restenosis. Circulation 1994;90:2402–13.
25. Shi Y, Fard A, Galeo A, et al. Transcatheter delivery of c-myc antisense oligomers reduces neointimal formation in a porcine model of coronary artery balloon injury. Circulation 1994;90:944–51.
26. Morishita R, Gibbons GH, Kaneda Y, Ogihara T, Dzau VJ. Novel in vitro gene transfer method for study of local modulators in vascular smooth muscle cells. Hypertension 1993;21:894–9.
27. Schneider MD, French BA. The advent of adenovirus gene therapy for cardiovascular disease. Circulation 1993;88:1937–42.
28. Plautz G, Nabel EG, Nabel GJ. Introduction of vascular smooth muscle cells expressing recombinant genes in vivo. Circulation 1991;83:578–83.
29. Conte MS, Birinyi LK, Miyata T, et al. Efficient repopulation of denuded rabbit arteries with autologous genetically modified endothelial cells. Circulation 1994;23:2161–9.