Endocarditis Risk of the USCI PDA Umbrella for Transcatheter Closure of Patent Ductus Arteriosus

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Background The USCI PDA Umbrella is a device to close patent ductus arteriosus (PDA) by a transcatheter technique. Human clinical trials have shown excellent efficacy in reducing or eliminating the PDA shunt, but concerns remain about the risk of infection with this device. The purpose of this study was to evaluate the risk of infection using an animal model.

Methods and Results Susceptibility to developing endocarditis was tested by injecting a single intravenous dose of group B streptococcus. Ten piglets with a closed ductus served as controls. Two of these developed valvular vegetations. PDA was produced in 19 animals by balloon dilation of the ductus. Seven of 7 animals with PDA at the time of bacterial injection developed endocarditis of the ductus and valvular vegetations. A PDA Umbrella was placed in the remaining 12 animals, and bacteria were injected 2 weeks after device implantation. Infection was evident in the PDA Umbrella only in the single animal in which the Umbrella had embolized and been left in the left pulmonary artery. Of the remaining 11 piglets, 2 had a significant residual leak, and all developed infection in the ductus and an additional valve. Similar to the control group, none of the animals with complete (n=8) or nearly complete (n=2) closure of the ductus by the PDA Umbrella had infection in or around the ductus, and only 1 had a valvular vegetation.

Conclusions In this animal model, presence of a significant PDA shunt (with or without a PDA Umbrella present) results in significantly increased susceptibility to endocarditis and endocarditis. The PDA Umbrella device does not appear to be susceptible to direct infection as early as 2 weeks after implantation if it is properly located in the ductus arteriosus.

Animals with no shunt or a trivial shunt are no more susceptible to developing endocarditis 2 weeks after PDA implantation than are controls. (Circulation. 1994; 90:2525-2528.)

Key Words • congenital heart disease • catheterization • PDA Umbrella

Patent ductus arteriosus (PDA) is a common congenital cardiovascular defect that can result in congestive heart failure or pulmonary hypertension if large and, even if small, is associated with a high risk of infective endocarditis.1,2 Indeed, about 45% of patients dying from PDA in the preantibiotic era died from infection rather than heart failure.3 Transcatheter closure of PDA using the USCI PDA Umbrella (an investigational device not commercially available in the United States) is a technique that has been under clinical investigation in the United States since 1981. Short- to intermediate-term results of this technique have been encouraging. In nearly all patients, successful placement essentially eliminates the hemodynamic effects of the PDA, but small leaks around the device are detectable by auscultation in approximately 7% of patients and by sensitive Doppler techniques in 11% to 20%.4-7 The risk of developing infection around the device or in the prosthetic material of the device is unknown. The purpose of this study was to use an animal model to evaluate the relative risk of developing endocarditis or endocarditis after a single injection of bacteria in piglets with an implanted PDA Umbrella.

Sham control animals and animals with unclosed PDAs were used as comparison groups.

Methods

Animal Model

A total of 30 piglets from five litters were entered into this study. Pregnant sows were transferred to the Animal Resources Facilities at the University of Nebraska Medical Center approximately 2 weeks before anticipated delivery and allowed to acclimate to the facilities.

Animal care and treatment complied with the animal welfare regulations of the institution and the FDA and conformed to the guiding principles of the American Physiological Society. Piglets remained with the sow until weaning at approximately 4 weeks of age since maternal factors in breast milk are important to development of the immune system in swine. Animals undergoing procedures before weaning were returned to the mother immediately upon recovery from anesthesia.

Animals from each litter were assigned to one of three groups. The control group (n=10) consisted of animals in which neither attempt was made to induce persistent patency of the PDA (n=2) or the attempt to create a persistent PDA failed. The second group consisted of animals in which PDA was created and no attempt was made to close the PDA (n=7), and the third group consisted of animals in which PDA was created and then a PDA Umbrella was later implanted (n=12).

Group assignments were not entirely random for logistical reasons. Because of the need for isolation of infected animals, facilities for only one litter at a time were available. Attempts were made to induce PDA in all animals except in 2 in the first litter. Those animals in which we were unable to achieve initial
opening of the ductus and those in which the PDA closed despite balloon dilation were assigned to the control group. Implantation of a PDA Umbrella was attempted in a number of the piglets from each subsequent litter, depending primarily on device availability. Comparisons of rates of infection in the different groups were analyzed using Fisher’s exact test. The differences were considered significant if the P value was <.05.

**Experimental PDA and PDA Umbrella Implantation**

Persistent patency of the PDA was induced by a modification of the method described by Lund et al. Briefly, prograde catheterization was performed percutaneously from the femoral vein in the piglets at 2 to 12 days of age. Animals were sedated with ketamine, and local anesthesia was used at the catheter insertion sites. The ductus in neonatal piglets is often probe patent at this early age even if functionally closed. A guide wire was passed through the pulmonary end of the ductus if possible and into the descending aorta. A dilation catheter was advanced over the guide wire from the venous side, and the ductus was dilated with a 4- to 6-mm-diameter balloon (NuMED) inflated to 3 to 4 atm. The size of the balloon used was dependent on the size of the piglet and the technical ability to push the balloon catheter through the probe-patent PDA. Animals that showed clinical signs of congestive heart failure were treated with oral or intramuscular furosemide, depending on the severity of symptoms. Animals without clinical evidence of PDA 12 to 20 days after initial dilation underwent repeat catheterization. If the PDA was closed at that time, the animal was assigned to the control group, and if the PDA was small, it was redilated with a 6-mm balloon. The technique for placement of the PDA Umbrellas was identical to that used in human clinical trials. All procedures were done under sterile conditions and with sterile equipment. Animals were given one dose of antibiotic during the implantation procedure and one dose after implantation.

**Microbiology Methods**

Group L streptococcus, originally isolated and characterized by Jones, was used as the infectious agent for this study. This organism has been shown to produce vegetative endocarditis in pigs when injected intravenously but is not normally pathogenic to humans. Long-term storage of the bacteria was accomplished by lyophilization. For each litter, a portion of the organisms was reconstituted and streaked onto a blood agar plate. A single colony was inoculated into 25 mL of brain-heart infusion medium and placed in a 37°C shaker bath. The turbidity of the culture was recorded at 1-hour intervals. When the culture reached the turbidity corresponding to 10⁶ colony-forming units/mL, 1-mL aliquots of the solution were placed in sterile microcentrifuge tubes and centrifuged at 1000 rpm for 5 minutes. The culture medium was decanted, and the pellets were resuspended in 1 mL of sterile saline. Each animal was injected in an ear vein with a single 1-mL dose of the bacteria. Purity of each batch of bacteria was confirmed by streaking for isolation at the commencement and end of each preparation cycle.

**Infection and Pathological Examination**

Susceptibility to infection was evaluated by injection of a single calibrated dose of group L streptococcus as described above shortly after weaning at 4 to 6 weeks of age. All animals had been weaned at this time and were healthy and self-sufficient. Animals in the PDA and PDA Umbrella implantation groups had an angiogram performed within 24 hours before the infection to confirm the status of the ductus or presence of any residual leaks around the PDA Umbrella. All of the animals in the PDA Umbrella group were infected 14 days after implantation.

Piglets were housed in separate cages after injection of the group L streptococcus and were handled with standard infection control procedures for strict isolation. Most of the animals became at least transiently lethargic. All animals were evaluated daily for signs of distress, but none became severely symptomatic before euthanasia 5 to 7 days after infection.

After euthanasia, the heart and lungs were removed as a block and fixed in neutral buffered 10% formaldehyde solution. The specimens were then sectioned and inspected carefully for evidence of gross vegetations on any of the cardiac valves or in the area of the PDA or PDA Umbrella. Sections from any suspicious areas as well as standard sections from each valve, both ends of the PDA, and both ends and the middle of any PDA Umbrella were submitted for paraffin embedding and light microscopic examination. Sections were stained with hematoxylin and eosin, Movat’s pentachrome, and Gram’s stains.

**Results**

**Angiography**

Angiograms just before infection were used to confirm the presence of PDA or to assess the degree of PDA closure by the PDA Umbrella in the noncontrol groups. None of the animals in the control group had a catheterization immediately before infection, but the PDA was confirmed closed in these animals by pathological examination. All animals in the PDA group had a patent ductus with a minimal diameter of 1 to 3 mm. In each of the animals in the PDA Umbrella group, the PDA Umbrella was angiographically in good position except in 1 animal in which the PDA Umbrella was known to have embolized to the left pulmonary artery at the time of implantation. No attempt had been made to retrieve that device, and the ductus was still open with significant residual shunting before the animal was killed. Three of the remaining 11 animals were found to have a significant residual leak around the PDA Umbrella, with clear opacification of the pulmonary arteries. Two additional animals had a trivial, barely detectable residual leak, with only a tiny stream of contrast medium seen in the main pulmonary artery (Fig 1). Six animals had complete closure of the ductus by the PDA Umbrella.

**Pathological Findings**

With the methods used in this study, we found evidence of endocarditis in 2 of the 10 control animals (inoculated without a PDA or PDA Umbrella). Both animals had small vegetations grossly evident on the mitral valve, with histological confirmation of the infectious nature of the lesions. Sections of other valves and the ends of the ductus did not disclose any evidence of infection.

The presence of significant PDA flow clearly increased susceptibility to developing endocarditis and endarteritis in this model. All of the piglets in the PDA group developed gross vegetations in and around the ductus within the 5- to 7-day study period. The vegetations in 6 of the 7 animals in this group were very large and extended into the main pulmonary artery (Fig 2). In addition, each of the animals in this group had evidence of infection of at least one cardiac valve, most often the pulmonic or tricuspid valve. The 4 piglets with an angiographically significant residual leak after PDA Umbrella implantation (1 with embolized device and 3 with device in the PDA) had findings similar to piglets with an unoccluded PDA—each had vegetations in or around the ductus, and 3 of the 4 had an additional valve infected. The rate of infection in animals with
more than trivial PDA flow (with or without a device in place) was significantly higher than the rate of infection in the control group ($P<.001$). The piglet with an “embolic” PDA Umbrella in the left pulmonary artery demonstrated a vegetation in the still widely patent ductus and was the only animal with microscopic evidence of infection of the PDA Umbrella material. None of the remaining 11 piglets had evidence of infection of the PDA Umbrella material.

The findings in the remaining 8 animals with complete (n=6) or nearly complete (n=2) closure of the ductus by the PDA Umbrella were similar to animals in the control group. None of these animals had evidence of infection of the PDA Umbrella or in the region of the ductus. One of these animals (with no residual shunt) had a small tricuspid valve vegetation. The rate of infection in animals with complete or nearly complete closure of the ductus by a PDA Umbrella was not significantly different from the rate of infection in the control group.

**Discussion**

The present study supports the current recommendations of investigators in the human trials of the PDA Umbrella with respect to infection prophylaxis, and the results of this animal study are consistent with the clinical findings to date. In this model, more than trivial PDA flow was clearly a major risk factor in determining susceptibility to infective endocarditis from a single dose of intravenous bacteria. The finding that animals with a PDA Umbrella in correct position for just 2 weeks and a completely or nearly completely occluded ductus were no more susceptible to infection than control animals is encouraging. The clinical evidence to date suggests that the risk of endocarditis after implantation of the USCI PDA Umbrella is low. We are aware of only two cases of endocarditis in such patients—one in whom infection developed very early after an implantation procedure during which prophylactic antibiotics were not given, and one wherein infection occurred late in association with a clearly clinically detectable residual leak.12 In most centers, the practice now is to give prophylactic antibiotics during the implantation procedure and then to instruct patients to observe routine endocarditis prophylaxis precautions for 6 to 12 months. If there is no evidence of residual shunting at that time, endocarditis prophylaxis precautions are stopped. Patients with clinically detectable residual shunts are advised to undergo further procedures to close the remaining PDA.

The best treatment for patients with very small residual shunts that can only be detected with Doppler echocardiography is more controversial. Two animals in this study simulated such a condition, and neither developed endocarditis. This is not a large enough group to determine the relative risk of endocarditis in this situation, but the finding is consistent with the apparent low risk of endocarditis in patients with a truly silent PDA.12 In our practice, we conservatively recommend continued endocarditis prophylaxis in this group.
of patients but do not feel that there is sufficient risk to routinely warrant additional procedures to attempt to close lesions that are not clinically detectable.

Animal models such as this cannot precisely mimic the conditions that may be present in humans, but this study does provide experimental support for continued use of the PDA Umbrella as a valid means of reducing or eliminating shunts while conveniently nullifying the additional risk of endocarditis in patients with a naturally patent ductus arteriosus.

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