Systemic polidocanol from intravenous or pressurized intrauterine administration produces reversible cardiovascular toxicity

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ABSTRACT

Objective: Fatal allergic responses and cardiac arrhythmias have been reported with the intravenous (IV) administration of polidocanol. We sought to identify the physiologic mechanism of systemic cardiovascular response after transcervical (TC) and IV administration of polidocanol.

Methods: We continuously monitored blood pressure (BP) and heart rate using an arterial line during IV and intraperitoneal (IP) administration of polidocanol solution (PS) and polidocanol doxycycline solution in female rats and TC and IP administration of polidocanol foam (PF) and PDF (TC only) in female baboons. We performed TC procedures using a catheter with (pressurized) and without (nonpressurized) balloon inflation. Baboons also underwent monitoring during IV PS administration with and without pretreatment with antihistamines. We performed cardiac echo and electrocardiograms during selected experiments. We defined a refractory hypotension as a sustained decrease of more than 30% from baseline that prevented delivery of the target dose.

Results: We found a dose-related increase in the proportion of baboons that developed refractory hypotension during TC administration of 5% PDF and PF, an effect confined to pressurized administration. The infusion of 0.5% PS in rats induced a rapid and dramatic refractory hypotension. The inclusion of doxycycline did not improve or deteriorate these outcomes, and doxycycline solution or saline (control) alone did not affect BP. All five female baboons that received up to 20 mL of 1% PS (200 mg) developed refractory hypotension. Pretreatment with diphenhydramine, ranitidine, or both did not block the refractory hypotension induced by IV administration of 1% PS (100 mg). In contrast, only one of the six female baboons treated with IP PF 400 mg developed a decrease of more than 30% in BP, and this response was not sustained. Cardiac echocardiography done in four baboons during TC treatment demonstrated a decrease in cardiac output as the physiologic mechanism of hypotension. We did not observe important changes on the electrocardiograms.

Conclusions: Adverse cardiovascular effects of polidocanol treatment occur owing to a direct myocardial effect of polidocanol and not as a result of a hypersensitivity reaction. Pressurized TC administration of PF results in refractory hypotension owing to endometrial vascular uptake of polidocanol and not as a result of uptake from peritoneal surfaces. (JVS–Vascular Science 2022;3:316-35.)

Clinical Relevance: Our experiments in rodent and nonhuman primates demonstrate that hypotension during polidocanol treatment occurs as a consequence of low cardiac output secondary to impaired biventricular function. The onset is acute, dose dependent, and precipitous, and resolves slowly upon discontinuation of the polidocanol infusion with appropriate supportive care. The physiologic features of this response are not explained by classical allergy, or by a complement-mediated pseudoallergic response. We propose that many of the adverse events reported after the therapeutic use of PS and PF occur owing to this direct effect on both the pulmonary vasculature and the myocardium and not as an allergic mechanism. Further investigations of this response mechanism may provide insight into potential therapeutic interventions to improve safety of polidocanol treatment.

Keywords: Sclerosis; Polidocanol; Ventricular function; Primates; Endometrium
The intravenous (IV) administration of a sclerosing agent provides a nonsurgical approach to the management of a variety of chronic vascular diseases including telangiectasias, reticular veins, and varicose veins. Detergent surfactants like polidocanol have regulatory approval in many countries as injectable solutions and foams for venous sclerosis. Sclerosing agents are also used off-label for other indications, including sclerosis of bone, renal, hepatic, and lymphatic cysts. Sclerosing agents in clinical use differ with respect to mechanism of action and toxicity profiles. They act by damaging the endothelium or epithelium; this damage results in collapse of the vessel or cyst followed by inflammation and collagen occlusion during repair.

Local tissue reactions at the injection site are the most common adverse events observed with injectable sclerosing agents. Although serious adverse effects are uncommon, a recent analysis of data from the World Health Organization pharmacovigilance database evaluated reports of six adverse event syndromes of interest: hypersensitivity reactions, arterial thromboembolic disorders, venous thromboembolic disorders, cardiac arrhythmias, visual/neurological disturbances, and skin ulcerations. Fatal allergic responses and cardiac arrhythmias have been reported for all sclerosing agents, including polidocanol.

Type I hypersensitivity responses develop when specific IgE antibodies, induced by a prior exposure to an antigen, cross-link and trigger the release of histamine and other inflammatory mediators upon re-exposure to the antigen. Type II hypersensitivity reactions develop when IgG or IgM antibodies recognize cell surface or extracellular matrix antigens and bind the Fc receptor of macrophages or activate the complement pathway directly. Szebeni proposed the term complement activation-related pseudoallergy (CARPA, or type III hypersensitivity) to differentiate hypersensitivity responses that activate complement independent of antibodies and mimic true allergic anaphylaxis pathways associated with first-time exposures to certain drugs and contrast agents. Because both true allergic responses and CARPA require the activation of a histamine receptor, strategies to prevent CARPA include the prophylactic administration of histamine receptor antagonists.

We have conducted early investigations in nonhuman primates evaluating the safety and efficacy of polidocanol (PF) and polidocanol doxycycline (PDF) foam sclerosis of the fallopian tube for the indication of nonsurgical permanent contraception. Doxycycline has independent activity as a sclerosing agent, so we tested PDF to determine if the combination could improve the rate of tubal occlusion observed with PF alone. We administer PF or PDF transcervically (TC) into the uterine cavity using a balloon catheter to occlude the cervix. Foam must fill the cavity before spilling out the fallopian tubes. In the baboon model, the small diameter fallopian tubes (approximately 100 microns) generate considerable resistance to flow that results in the pressurization of foam within the endometrial cavity. We discovered that some animals developed refractory hypotension, suggestive of severe anaphylaxis, during TC foam treatment, with findings similar to those previously reported during vascular sclerosis procedures with polidocanol. This finding led us to conduct a series of experiments to mechanistically explain the physiologic basis for the adverse cardiovascular response to polidocanol treatment.

Methods

Animal care

The animals used in these experiments include not only nonhuman primates, but also rats, which makes it possible to increase the size of animal numbers for different exploratory approaches because of the greater availability of small animals for in vivo study.

The Institutional Animal Care and Use Committees (IACUC) at the Oregon National Primate Research Center (ONPRC) and Kenya Institute of Primate Research approved all of the baboon procedures at their respective institutions. Animal husbandry provided by both institutions is in accord with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals, with all animals maintained in social housing groups. We conducted all of the surgical procedures under general anesthesia using IACUC-approved protocols. Adult female baboons (Papio anubis, Papio hamadryus) aged 12 ± 7 years and weighing 17 ± 8 kg used in the study underwent sedation with ketamine (10 mg/kg IM; Putney, Dublin, OH) before endotracheal intubation and induction and maintenance of general anesthesia with isoflurane (WI, Boise, ID) inhalation (see the Supplementary materials for additional details).

Rodent studies received IACUC approval at ONPRC. We obtained healthy adult (250-360 g) female Sprague-Dawley rats from a vendor (Charles River Laboratories, Wilmington, MA). Trained veterinary staff performed all
of the procedures under mask general anesthesia with isoflurane.

Preparation of polidocanol solution and foam
We obtained bulk polidocanol from two different commercial sources, Sigma (St Louis, MO) (research grade) and LGM Pharma (Boca Raton, FL) (pharmaceutical grade). Detailed analyses comparing the two sources showed no important chemical differences (data not shown). We prepared a polidocanol solution (PS) (weight/volume) by warming bulk polidocanol to 37°C for 10 minutes before dilution with Dulbecco’s phosphate-buffered saline (DPBS) to the required volume. A 5% PS contains 50 mg of polidocanol in 1 mL of DPBS; a 1% solution contained 10 mg/mL, and a 0.5% solution contains 5 mg/mL. To prepare polidocanol foam (PF), we draw 1 mL of the PS (1 mL) into a 5-mL syringe, and fill a second 5-mL syringe with 4 mL of air. We then used a modified Tessari technique to generate foam by passing the air and solution mixture back and forth 20 times through a 5-μm syringe filter between the two syringes with Luer lock fittings. On the final pass, this process results in 5 mL of foam collected in one syringe for injection. The process is repeated for subsequent 5-mL aliquots. Some animals received a combined polidocanol/doxycycline solution or foam (PDF). To prepare this, we added 100 mg of doxycycline powder (Novaplus, Fresenius Kabi, Lake Zurich, IL) to 4 mL of PS, agitating the solution until dissolved before generating foam.

IV and intraperitoneal administration of PS in rats
We used rats to compare the (1) cardiovascular effects of different PS (eg, research grade or pharmaceutical grade; doxycycline or no doxycycline) when administered IV and (2) cardiovascular effects of the same dose of PS administered IV and intraperitoneally (IP). We used solutions rather than foams in these experiments to eliminate the potential confounding factor of air embolism. We evaluated doxycycline, because we sought to determine if this agent changed the cardiovascular effects of polidocanol. To minimize the number of animals used, data from some rats were used in multiple comparisons.

Anesthetized females underwent dissection of the femoral triangle to provide exposure for placement of a 2F polyurethane medical tubing into the femoral vein for IV access, and another catheter into the femoral artery for continuous monitoring of blood pressure (BP). For IP infusions, we placed an 18G angiocath directly through the abdominal wall into the peritoneal cavity. We used a syringe pump to infuse all test solutions IV at a rate of 0.1 mL/min through the femoral vein. All of the experiments used the same sequence: (1) baseline (saline for 3 minutes [0.3 mL]); challenge 1 (test agent—polidocanol, doxycycline, or combination for 5 minutes [0.5 mL]); recovery 1 (no infusion for up to 7 minutes [minimum of 3 minutes if no change from baseline during challenge 1]; Challenge 2 (same test agent as Challenge 1 for 2 minutes [0.2 mL]); and recovery 2 (5-20 minutes).

Rats (n = 6 per group) received one of the following IV test agents: (1) PS 0.5% (research grade source); (2) PS 0.5% (pharmaceutical grade source); (3) Asclera (US Food and Drug Administration-approved 0.5% PS product); (4) PS 0.5% with a doxycycline 25 mg/mL solution (polidocanol doxycycline) (research grade source); (5) polidocanol doxycycline (pharmaceutical grade source); (6) doxycycline solution (25 mg/mL saline); or (7) DPBS (control). Active treatments provided 3.5 mg polidocanol and/or 17.5 mg doxycycline. Rats undergoing IP administration received only PS 0.5% (pharmaceutical grade source).

TC administration of PF in baboons
We performed cervical dilation, placed a 7F silicone hysterosalpingogram (HSG) balloon catheter (3-CHSG-703000; Cook, Bloomington, IN) into the uterine cavity of female baboons under ultrasound guidance, evaluated tubal patency, and infused PF through the catheter into the uterine cavity as previously described. Inflation of the balloon of the HSG catheter in the lower uterine segment seals the cavity and prevents leakage of the administered agent through the cervix as uterine pressure increases to a level sufficient to overcome the resistance of flow for movement of the solution or foam into the fallopian tubes. TC administration of the solution or foam without balloon inflation allows leakage through the cervix and prevents uterine cavity pressurization and tubal delivery.

To evaluate the effect of polidocanol dose, we performed TC administration of PDF with the HSG balloon inflated (pressurized) in one baboon group (n = 5). Among these animals, five received a target dose of 20 mL (200 mg polidocanol) and four a target dose of 40 mL (400 mg). We discontinued foam administration upon reaching a prespecified stopping point of a 30% decrease from baseline in mean arterial pressure (MAP). Animals underwent electrocardiograms (ECG) during these procedures.

We then performed a controlled experiment in baboons to directly compare the effects of pressurized and nonpressurized foam delivery. Females (n = 5) received 5% PF using two different routes of administration in the following sequence: (1) TC nonpressurized (eg, Cook HSG catheter placed without inflation of balloon) and (2) TC pressurized (eg, Cook HSG catheter placed with inflation of balloon). We conducted the two treatments approximately 1 month apart at the same menstrual cycle phase (peak tumescence) to control for hormonal effects. The females received up to 40 mL of 5% PF (400 mg polidocanol) during each procedure. We discontinued the foam administration upon
reaching a prespecified stopping point of a 30% decrease from baseline in MAP.

The same investigator performed all of the PDF and PF infusions, delivering foam by hand at an approximate rate of 2 mL/minute.

**IP administration of PF**

In addition to uptake from endometrial blood vessels, polidocanol could enter the vascular space by direct absorption from peritoneal surfaces after spillage from the fallopian tubes during TC procedures. To determine whether clinically important cardiovascular effects result from peritoneal uptake, we performed direct IP injection of polidocanol. We used two approaches for IP delivery, namely, laparoscopic and direct injection. For laparoscopic delivery, anesthetized female baboons prepared for cardiovascular monitoring underwent insertion of a Cook HSG catheter through an accessory port with placement of the tip into the pouch of Douglas under direct visualization. After allowing the CO₂ pneumoperitoneum to evacuate spontaneously, the investigator administered up to 40 mL (400 mg) of 5% PF through the catheter in 5-mL aliquots (approximately 2 mL/min). The catheter was then removed, and incisions closed. Other anesthetized females underwent blind placement of an 18G angiocath through the anterior abdominal wall, with direct delivery of the same dose.

**IV administration of PS and antihistamines in baboons**

Because TC administration of PF results in unpredictable vascular uptake of polidocanol and introduces air bubbles as an additional variable, we delivered polidocanol as an IV infusion to study the effects of direct vascular uptake of polidocanol and introduces air bubbles as an additional variable, we delivered polidocanol. We used two approaches for IP delivery, namely, laparoscopic and direct injection. For laparoscopic delivery, anesthetized female baboons prepared for cardiovascular monitoring underwent insertion of a Cook HSG catheter through an accessory port with placement of the tip into the pouch of Douglas under direct visualization. After allowing the CO₂ pneumoperitoneum to evacuate spontaneously, the investigator administered up to 40 mL (400 mg) of 5% PF through the catheter in 5-mL aliquots (approximately 2 mL/min). The catheter was then removed, and incisions closed. Other anesthetized females underwent blind placement of an 18G angiocath through the anterior abdominal wall, with direct delivery of the same dose.

**Cardiovascular and uterine pressure monitoring**

During all of the experiments, weestablished baseline data for at least 10 minutes and then monitored animals continuously during administration of foam or solution and for at least 30 minutes after the infusion. We used a 2F polyurethane medical tubing to cannulate the femoral artery and connected this to the Deltran transducer using a Luer adapter. During baboon experiments, we used the additional channels and Deltran transducers to simultaneously record intrauterine pressure (using a 2F polyurethane catheter placed within the uterine cavity) and pressure within the delivery catheter.

**Noninvasive cardiovascular monitoring.** During baboon procedures performed in the surgical suites at ONPRC, we recorded a number of parameters using the available Anesthesia monitoring equipment (Digicare Biomedical Technology, Inc., Boynton Beach, FL). These included end-tidal CO₂ (EtCO₂), respiratory rate, and O₂ sat. We also recorded noninvasive measurements of SBP and DBP using a pediatric cuff. During the baboon PDF TC infusions only, we collected 12-lead ECGs (Cardio7.2, Bionet Co, Tustin, CA) at baseline and every 5 minutes throughout treatment and during recovery. For experiments conducted at Kenya IPR and for some baboon and all rat procedures at ONPRC, we used portable monitors for O₂ sat (Nonin PalmSAT 2500 Digital Hand-Held Pulse Oximeter) and EtCO₂ (Masimo EMMA Mainstream Capnograph Kit). We did not collect data on EtCO₂ in rats.

**Echocardiograms.** An imaging team blinded to treatment-related variables performed transthoracic echocardiography (Vivid E95, GE Health Care, Chicago, IL) during selected TC baboon procedures at ONPRC at the following stages: stage 1, baseline; stage 2, upon completion of first 100-mg polidocanol administration; stage 3, upon completion of the peak dose of polidocanol; stage 4, 15 minutes after completion of administration; and stage 5, 25 minutes after completion of administration. All measurements followed guidelines for adult echocardiographic measurement from the American Society of Echocardiography. Systemic vascular resistance (SVR) was calculated as the difference between the MAP from BP
measurement and the right atrial pressure from inferior vena cava diameter and respirophasic variation, divided by the cardiac output derived from the product of HR and stroke volume by left ventricular (LV) outflow tract diameter-time velocity integral product. An index of pulmonary vascular resistance (PVR) was calculated without estimation of left-sided filling pressures by dividing the pulmonary artery peak systolic pressure (derived from tricuspid regurgitation jet velocity and inferior vena cava measurements) by the cardiac output. Peak contrast enhancement within the ventricular cavities, when observed after injection of sclerosing agents, was quantified by imaging with low-mechanical index (0.14) power modulation imaging at a dynamic range of 50 dB. Video intensity was measured from regions of interest in the ventricular cavities. Because treatments varied between animals, all data represent animal-specific findings.

**Intrauterine pressure monitoring.** To measure pressure within the uterine cavity during foam administration, we passed a 2F polyurethane medical tubing through the delivery channel of the HSG catheter. The tip extended 1 cm beyond the end of the catheter. We connected this to the Deltran transducer and recoding system using a Luer adapter.

**Data analysis**

For IV administration of PS in baboons and rats, we calculated group means and standard deviations, and compared treatment time points using analysis of variance. For the TC experiments in baboons, we present individual data only without summary statistics or statistical comparisons owing to the variation in treatment response, and inability to make comparison between dose and techniques groups.

**RESULTS**

Severe adverse effects of TC administration of PF in baboons are dose dependent and occur during administration with uterine cavity pressurization. In the dose experiment, all four females in the 20-mL (200 mg polidocanol) PDF group received the full target dose. The SBP, DBP, and mean BP increased with the initiation of the PDF infusion, and this was followed by a steep decrease, with three of the four reaching a MAP nadir of less than 70% of baseline by the end of the infusion or during recovery (Fig 1, A, Supplementary Table I). All of the animals recovered within 30 minutes without further intervention. In contrast, four of the five animals in the 40-mL (400 mg) dose group experienced a treatment-ending decrease in BP before received the full target dose (Fig 1, B, Supplementary Table I), after developing a clinically important decrease in BP during the procedure. Two of these females received IV epinephrine (total 0.2 mg) for circulatory support, and the other two recovered without additional intervention. We did not observe clinically important changes in HR or O2 sat in any of the animals (Fig 1, Supplementary Tables II and III). However, we failed to record data with the pulse oximeter at critical time points in some animals, likely as a result of poor perfusion, because this occurred during episodes when we could also not record BP. However, the ECG showed pulseless electrical activity during these episodes of poor perfusion, ruling out asystole as the physiologic mechanism for the bradycardia (Fig 2).

To compare the effect of uterine pressurization, five other female baboons underwent TC administration of up to 40 mL (400 mg) 5% PF through a Cook HSG catheter without and with inflation of the balloon. During the first procedure with nonpressurized foam, all five tolerated the full 400-mg dose of polidocanol. The mean uterine cavity pressure during foam infusion remained less than 100 mm Hg. Although two animals demonstrated a more than 30% decrease in MAP, this occurred only at or after completion of the foam infusion, and resolved rapidly without intervention. In contrast, the same five animals undergoing pressurized foam delivery (uterine pressure >150 mm Hg) experienced a more than 30% decrease in MAP during or after the infusion (Fig 3, Supplementary Table IV). The severity of this decrease required premature termination of the PF infusion before reaching the target dose in all four animals. Although all of the animals recovered without intervention, hypotension persisted for more than 30 minutes in most cases, with the magnitude of effect related to total dose received. The animal that tolerated the full 400-mg dose experienced only a transient decrease in MAP during recovery. Consistent with the dose experiment, we did not record important changes in HR or O2 sat in any of the animals with either treatment. Fig 4 provides actual details of the relationship between uterine pressure and BP during pressurized and nonpressurized PF delivery in representative animals. Treatment with pressurized PF resulted in a slight increase in BP in most animals, followed by a decrease in MAP associated with a narrowing of the pulse pressure. During recovery, the pulse pressure and MAP gradually increased. As expected, intrauterine pressure was greater during pressurized foam delivery, and this finding was associated with more significant changes in BP. We were unable to record intrauterine pressure during the nonpressurized treatment in baboon xxx16; the investigator subjectively reported high resistance during foam administration and did not note the expected spillage of foam through the cervix. This female experienced a more than 30% decrease at the end of treatment (Supplementary Table IV).

IV administration of PS in rats results in reversible hypotension: Doxycycline has no effect. To compare the effects of PS with and without doxycycline directly, we performed experiments in rats using controlled IV administration to have sufficient animal numbers for
statistical comparisons of the results and to eliminate potential confounding owing to air bubbles in foam. During the initial control infusion of saline, the HR and BP (SBP, DBP, MAP) did not change from baseline. In contrast, IV infusion of polidocanol, with or without doxycycline, resulted in a rapid decrease in both the BP and the HR, which recovered rapidly with no important differences between polidocanol sources (Fig 5). These effects of polidocanol were transient with recovery seen at 5 minutes. With most polidocanol treatments, BP changes reached or approached a 50% decrease from baseline and there was no worsening of the effect with repeat dosing. In contrast, the administration of doxycycline alone did not result in any effect on the BP or HR.

Adverse cardiovascular effects occur with IV administration of PS in baboons, and antihistamine treatment does not mitigate or prevent these findings. Having determined that doxycycline did not contribute to the cardiovascular effects in rats, we performed additional experiments with the IV administration of polidocanol only in baboons. Similar to rats, the IV administration of PS in baboons resulted in a rapid and dose-related effects on BP, HR, EtCO₂ but not O₂ sat (Fig 6). All of the animals experienced a more than 50% decrease in the pulse pressure (range, 52%-92%). The effects reversed after the discontinuation of treatment in all six females.

To test the hypothesis that histamine release mediated the adverse cardiovascular effects of polidocanol, we pre-treated anesthetized baboons with diphenhydramine.
(HIB), ranitidine (H2B), both diphenhydramine and ranitidine (H1B+H2B), or no additional treatment (C) before the administration of 1% PS through a peripheral IV catheter via an infusion pump. All of the antihistamine-treated females also received pretreatment with cromolyn sodium 20 mg by nebulizer. Similar to our other experiments with IV PS and pressurized TC PF, we found a dose-related decrease in the BP. Although this change was not associated with a decrease in the HR in most animals, we observed a decrease in the ETCO₂ suggestive of decreased perfusion. Neither treatment with H1B or H2B prevented these adverse effects, with broad overlap between the treatment groups. Notably, the most severe changes occurred with combined H1B+H2B (Fig 7).

IP administration of PF does not result in adverse hemodynamic effects. During TC delivery, polidocanol could enter the vasculature through endometrial blood vessels and lymphatics or as a result of peritoneal...

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**Fig 2.** Representative electrocardiogram (ECG) changes during transcervical (TC) delivery of polidocanol foam (PF). Although baboons xxx93 (top) and xxx94 (bottom) exhibited refractory hypotension with no recordable blood pressure (BP) or pulse in response to PF infusion, we observed continued electrical activity on ECG throughout the procedure. (Left) Baseline ECG in leads I, II, and III before the start of the infusion. (Right) ECG in leads I, II, and III during episodes when no pulse or BP recorded with arterial line (pulseless electrical activity).
absorption after spilling through the fallopian tubes. To further evaluate our hypothesis that adverse cardiovascular effects result from endometrial uptake of polidocanol during TC administration of pressurized PF, and not from peritoneal uptake, we performed direct IP administration in rats and baboons.

Rats that received a 0.1-mL/min IV infusion of 0.5% PS developed an approximately 50% decrease in BP from baseline, whereas animals that received the same treatment and dose IP showed no change in BP \((P < .05)\) (Fig 8, A).

Four baboons received IP administration of 5% PF (40 mL, 400 mg) at the time of laparoscopy, and two additional females through a direct IP injection. Three of the four females treated at the time of laparoscopy tolerated the target 40-mL 5% PF dose without clinically important changes in MAP (Fig 8, B, black closed circles). One female received only 30 mL of PF after reaching the stopping point of a 30% decrease (Fig 8, B, black open circles). Notably, the administration of foam was observed subjectively to require considerable force in this female not perceived in the other three, suggesting embedment of the catheter tip in the peritoneal surface, resulting in pressurization. Moreover, the decrease in MAP was transient with recovery beginning within 5 minutes of discontinuation and complete at 30 minutes.
The two animals that received direct IP injections showed no clinically important changes in BP (Fig 8, B, blue circles).

Adverse cardiovascular effects of pressurized TC administration of PF in baboon. We simultaneously performed transthoracic echocardiography during pressurized TC administration of up to 40 mL of 5% PF delivered with a Cook HSG catheter with the balloon inflated on four additional female baboons. We selected these females because we had noted significant vascular uptake of contrast agent and tubal occlusion during prior HSG evaluations, but two animals (xxx43, xxx49) demonstrated tubal patency during the echo.
procedures, with one of these (xxx49) showing no apparent vascular uptake. All but one animal (xxx91) received pretreatment with diphenhydramine 25 mg IV and cromolyn sodium 20 mg by nebulizer before the polidocanol infusion. For all echo measurements, animal xxx49, the female with tubal patency and no evidence of significant vascular uptake, tended to have less adverse effects on LV function than the other animals. We did not see any evidence of an effect of antihistamine treatment.

Arterial pressure (MAP) tended to increase early during the PF infusion but then returned to baseline values, whereas SVR, which takes into account cardiac output, increased markedly during PF infusion and remained high in all three animals that demonstrated vascular uptake during the TC infusion (Fig 9, A and B). Stroke volume, whether measured by LV outflow tract flow or by Simpson’s biplane, decreased early during PF injection in the three animals with vascular uptake, and remained low, resulting in a decreased cardiac output that persisted long after the injection was completed (Fig 9, C and D). Other metrics of LV function such as fractional shortening and LV ejection fraction showed similar patterns with a severe decrease in affected animals, which did not fully recover by the final study (Fig 9, E and F). Decreased function was associated with an increased in LV end-systolic dimension without evidence for acute dilation by end-diastolic dimension (Fig 9, G and H). LV myocardial work, an index that takes into account afterload, initially increased in several animals during PF infusion, but eventually decreased to values below baseline in all animals that had evidence of decreased LV function (Fig 9, I). These findings imply that decrease in LV function early during PF infusion may be influenced by load but progressive worsening occurs owing to a direct decrease in myocardial performance. We observed no major changes in LV diastolic measurements, including early diastolic velocity of the mitral annulus (e') nor estimated LV filling pressure by the ratio of transmural E/e' (data not shown).
We found similar temporal patterns of right ventricular (RV) dysfunction as seen for the LV. A progressive decrease in RV peak systolic velocity of the lateral tricuspid annulus (S’), tricuspid annular plane excursion, and RV fractional area change were seen during active PF infusion (Fig 10, A-C). Similar to what was found for the systemic circulation, PVR increased more than pulmonary artery systolic pressure secondary to changes in stroke volume (Fig 10, D and E). Again, animal XXX49 tended to have less severe hemodynamic and functional deficits than other animals. RV myocardial work remained either unchanged or decreased, implying again a mixed effect of load-related decrease in function early and impaired myocardial performance late (Fig 10, F).

Contrast enhancement in the form of cavitation nuclei, suggestive of PF bubbles or droplets, were observed only after initiating PF injection and were seen only in the right heart chambers with no transition of contrast enhancement to the left sided chambers (Fig 10, G and H). Contrast enhancement was not observed in animal xxx49.

DISCUSSION

PS and foam are approved agents for venous sclerosis, and are used off-label for a variety of indications. Our group has reported that TC delivery of PF will result in de-epithelialization of the intramural portion of the fallopian tube in nonhuman primates and formation of a permanent collagen scar. We have performed a proof-of-concept contraception study in baboons that demonstrated prevention of pregnancy in 80% of the females that received a single treatment with 5% PF delivered using a standard HSG catheter. However, TC administration of foam results in considerable pressurization of the endometrial cavity as the small fallopian tube diameter of the baboon results in high resistance to flow. This pressurization results in the uptake of fluids and foam into the extensive vascular plexus of the endometrium. Vascular uptake of fluids is a known complication of hysteroscopic surgery in women, with deaths reported. The considerable vascular remodeling that occurs in the endometrium during the menstrual cycle results in a loss of microvascular endothelial integrity that contributes to this process, but pressurization plays a critical role. Our data suggest that, during TC PF procedures in baboons, the vascular uptake of polidocanol that occurs as a result of uterine cavity pressurization is the main contributor to cardiovascular toxicity.

Because TC delivery of PF represents a new route of delivery, we conducted toxicology studies to evaluate safety of the approach to support future clinical trials of PF for permanent contraception. We found significant dose-dependent adverse cardiovascular effects with pressurized TC administration of 5% PF and PDF, an alternative formulation. Because the 5.0% concentration of polidocanol is considerably higher than the 0.5% and 1.0% formulations currently approved for clinical use for venous sclerosis, and we do not have a complete understanding of the pharmacokinetics of polidocanol uptake with intrauterine administration, we conducted controlled experiments of dose and rate using IV infusion. Our results in rats confirm that adverse hemodynamic effects occur rapidly during IV administration, and that this effect is not related to or increased by the addition of doxycycline. The direct IV administration of PS in baboons produces the same response. In contrast, TC administration of PF without inflation of the balloon, which permits
excess foam to drain through the cervix without pressurization, or direct IP administration of PF do not result in severe adverse hemodynamic effects. These experiments support the premise that pressurization within the uterine cavity results in endometrial vascular uptake of PF that generates the observed effects. To mitigate the adverse effects and improve safety and efficacy, a selective catheter system to deliver foam to the fallopian tubes without cavity pressurization is under development to decrease endometrial vascular uptake.

Pressurization of the uterine cavity occurs during many gynecologic surgical (eg, hysteroscopy) and imaging (eg, HSG) procedures and is not associated with adverse cardiovascular effects. All of the baboons used in our

**Fig 7.** Antihistamine treatment does not mitigate the adverse cardiovascular effects of intravenous (IV) polidocanol solution (PS). Baboons were pretreated with diphenhydramine (H1B), ranitidine (H2B), or both (H1B + H2B), or received no pretreatment before IV administration of 1% PS (1 mL/min, target dose 10 mL = 100 mg). Administration of PS resulted in a rapid dose-dependent decrease in blood pressure (BP) and respiratory rate, neither of which was prevented by antihistamine pretreatment. Data (normalized to baseline) presented as mean ± standard deviation (normalized to percent baseline). n = 3-6 per group. EtCO2, end-tidal CO2.

**Fig 8.** Intraperitoneal (IP) administration of polidocanol foam (PF) does not result in adverse blood pressure (BP) effects. (A) Rats (n = 6) received 0.5% PS intravenously (IV) or IP. IV administration resulted in a reversible decrease in the mean arterial pressure (MAP), an effect not seen with IP administration. Data represent the start of each period: saline for 3 minutes (0.3 mL); period 1: 0.5% PS for 5 minutes (0.5 mL); period 2: no infusion (5-7 minutes); period 3: 0.5% PS for 2 minutes (0.2 mL); and period 4: recovery (5-20 minutes). Data are presented as mean ± standard deviation (normalized to percent baseline). (B) Baboons received up to 40 mL of 5% foam following laparoscopy (black circles, n = 4) or through a direct IP injection (blue circles, n = 2). PF1-8 indicate successive 5-mL (50-mg) aliquots of PF. Post-treatment (Tx) nadir reflects the lowest MAP reading after Tx and 30 minutes, the reading 30 minutes after completion of the infusion. Data reflect start of each period normalized to baseline. Red symbol indicates premature discontinuation PF infusion in one female (laparoscopic group, open black circle) owing to a more than 30% decrease in the MAP. Recovery was prompt.
Experiments underwent a baseline HSG procedure before administration of PF; we did not observe adverse HR and BP changes during these examinations (data not shown).

Although allergic responses after polidocanol administration in humans have been reported, the transient and dose-related hemodynamic features we observed in animals not previously exposed to polidocanol are not consistent with a type I or II hypersensitivity reaction. To explore the hypothesis of a potential CARPA effect, we pretreated baboons with histamine receptor blockers before IV PS. Our results did not support a benefit of HR1 or HR2 blockade. Rather, antihistamine treatment tended to result in more severe adverse changes.

We performed echocardiography to provide insights into the cardiovascular toxicity of polidocanol. The integration of echocardiographic and hemodynamic data from these experiments is complex. We can conclude unequivocally that gaseous or emulsion-based bodies, likely containing polidocanol, are partitioning in a pressure-dependent fashion into the venous circulation. There is no transition to the left-sided chambers, indicating either that these particles are sufficiently large to lodge in the pulmonary circulation, are taken up by other mechanisms (e.g., pulmonary macrophages or C'-mediated binding), or lose their gas volume during pulmonary transit. The absence of left-sided contrast does not exclude the transit of polidocanol to the systemic circulation, only that any transit is not in the form of a large gas-containing particle that can be detected by ultrasound techniques designed to receive cavitation energy. LV and RV dysfunction with subsequent decrease in cardiac output are seen very early in the administration. Based on the changes in PVR and SVR, and the temporal changes in RV and LV myocardial work, it is likely that afterload mismatch played a role in the decrease in ventricular function early during the infusions. In particular, the RV is less tolerant of acute

Fig 9. Transthoracic echocardiography during pressurized transcervical (TC) administration of 5% polidocanol foam (PF) revealed LV dysfunction. Mean arterial pressure (A), systemic vascular resistance (B), stroke volume (C), cardiac output (D), fractional shortening (E), left ventricular ejection fraction (F), left ventricular end diastolic dimension (G), left ventricular end-systolic dimension (H), and left ventricular myocardial work (I). Two animals (xxx91, xxx51) demonstrated prominent vascular uptake of contrast agent and tubal occlusion during hysterosalpingogram (HSG), one (xxx43) prominent vascular uptake and tubal patency, and one (xxx49) tubal patency with no apparent vascular uptake. For all echo measurements, animal xxx49, the female with tubal patency and no evidence of significant vascular uptake, tended to have less adverse effects on LV function than the other animals. LV, left ventricular; LVEF, left ventricular ejection fraction; LVIDd, LV end-diastolic dimension; LVIDs, LV end-systolic dimension; MAP, mean arterial pressure; SVR, systemic vascular resistance.
increases in afterload and the degree of PVR that we observed was severe (>15 Woods units) in animals that also had severe decrease in ventricular function. However, direct effects on ventricular function are very likely, particularly late in the infusion, based on the severe decrease in LV function at a time when SVR was increased but systemic BP, based on myocardial work values, was not. The relative sparing from adverse effects in the animal lacking evidence for contrast enhancement provides a direct link between blood pool absorption of polidocanol and adverse cardiovascular effects. It is unlikely that physical obstruction of the pulmonary microcirculation from large gas bubbles was the primary cause of cardiovascular changes. Massive microvascular obstruction would have likely resulted in decrease in LV dimensions, severe septal shift, and a decrease in E/e', which were not seen.

The changes in SVR are complex. It is possible that PD-related increases in SVR contributed to impairment in ventricular performance. However, SVR is also known to increase in response to an acute decrease in cardiac output to maintain perfusion pressure in vital organs. The finding of moderate to severe LV dysfunction in the presence of high SVR but relatively normal SBP implies that direct changes to LV function were dominant mechanisms for the high SVR. During clinical administration of polidocanol, an increase in BP and HR may indicate the potential for rapid deterioration and prompt termination of treatment. Alternatively, echocardiographic monitoring for systemic absorption can also be considered as a potential safety measure.

Thus, our experimental results demonstrate that polidocanol infusion results in adverse cardiovascular changes owing to vascular and probably direct...
myocardial toxicity. Currently, we do not understand the cellular mechanism of this toxicity, but it seems to be dose related, transient, and reversible. Palmitoyl carnitine, a chemically similar long-chain fatty alcohol surfactant has been shown to irreversibly inhibit Na\(^+\)-K\(^+\)-ATPase in canine cardiac myocyte sarcolemma.\(^{26}\) Oexle et al\(^{27}\) reported that polidocanol perfusion of the guinea pig heart caused an irreversible decrease in frequency and delay of atrioventricular and intraventricular conduction consistent with blockade of fast sodium channels. Our results from ECG monitoring during polidocanol treatment of baboons do not support abnormality of the conduction system; we observed sinus rhythm even during periods of profound hypoperfusion. However, the decrease in BP with a decrease, rather than compensatory increase, in the HR in rats suggests a conduction abnormality may occur in rodents, consistent with the effects observed by Oexle et al. We did not conduct echocardiogram studies in rats.

Cardiac arrest and myocardial infarction after PF sclerotherapy have been reported.\(^{18,28,29}\) A major weakness of our study is that we did not obtain troponin or other enzymes to evaluate myocardial damage and we do not have polidocanol blood concentrations. We did not observe any residual clinical signs of behavioral features (eg, decreased activity, pain, poor feeding) after recovery suggestive of permanent cardiovascular compromise among any of the treated animals, even those with significantly prolonged treatment-related hypotension. Furthermore, we conducted complete necropsy evaluations in all of the animals reported in this study, which revealed no abnormal gross or histologic abnormalities in the heart.

We did not evaluate the potential impact of sex differences, because we used female animals for all of our experiments. Further experiments are needed to confirm whether the cardiovascular effects of intravascular administration of polidocanol are generalizable to male animals.

Polidocanol enters the systemic circulation during TC intrauterine administration with pressurization. Although pressurization does not normally occur with administration of PF or PS during administration with approved routes of IV administration, it may occur with some off-label uses. For example, Gupta et al\(^{30}\) reported a case of life-threatening cardiac collapse in a 3-year-old boy treated with 10 mL of 3% PS for an aneurysmal bone cyst of the femur. The child developed tachycardia and a decrease in BP from 96/52 mm Hg to 80/30 mm Hg after injection of the initial 3 mL. The clinicians waited 15 minutes for the BP to stabilize, and then continued the infusion. This resulted in a BP decrease from 100/70 mm Hg to 50/20 mm Hg and ventricular tachycardia, findings similar to those observed during pressurized TC PF administration and IV PS in baboons. The child was treated with amiodarone and supportive care, and stabilized within 20 to 30 minutes.

In summary, our experiments demonstrate that hypotension during polidocanol treatment occurs as a consequence of low cardiac output secondary to impaired biventricular function. The onset is acute, dose dependent and precipitous, and resolves slowly upon discontinuation of the polidocanol infusion with appropriate supportive care. The physiologic features of this response are not explained by classical allergy or by CARPA. We propose that many of the adverse events reported following therapeutic use of PS and PF occur owing to this direct effect on both the pulmonary vasculature and the myocardium, and not as an allergic mechanism. Further investigations of this response mechanism may provide insight into potential therapeutic interventions to improve safety of polidocanol treatment.

**AUTHOR CONTRIBUTIONS**

Conception and design: JJ, OS, JL

Analysis and interpretation: JJ, PL, JC, JL

Data collection: JJ, PL, MR, JC, SY, EM, TG, JH, JL

Writing the article: JJ

Critical review of the article: JJ, PL, MR, JC, SY, EM, TG, JH, OS, JL

Final approval of the article: JJ, PL, MR, JC, SY, EM, TG, JH, OS, JL

Statistical analysis: JJ

Obtained funding: JJ

Overall responsibility: JJ

**REFERENCES**

1. Farah MH, Nayfeh T, Urtecho M, Hasan B, Amin M, Sen I, et al. A systematic review supporting the Society for Vascular Surgery, the American Venous Forum, and the American Vein and Lymphatic Society guidelines on the management of varicose veins. J Vasc Surg Venous Lympath Disord 2022;10:1155-71.

2. Deventer N, Deventer N, Gosheger G, de Vaal M, Vogt B, Budyń T. Current strategies for the treatment of solitary and aneurysmal bone cysts: a review of the literature. J Bone Oncol 2021;10:100384.

3. Cardenas-Vargas MI, Ortiz MI, Izquierdo-Vega J, Díaz-Zamudio M. Sustained volume decreases in simple renal cysts after sclerotherapy using NBCA with or without hydrodissection. J Interv Med 2021;4:15-20.

4. Shimizu T, Yoshioka M, Kaneya Y, Kanda T, Aoki Y, Kondo R et al. Management of simple hepatic cyst. J Nippon Med Sch 2022;89:2-8.

5. Parrado RH, Thomas CS, Countryman D. Successful treatment of inguinal lymphocele after angiomyomatous hamartoma resection during inguinal hernia repair. Wounds 2021;33:E42-S.

6. Duffy DM. Sclerosants: a comparative review. Dermatol Surg 2010;36(Suppl 2):1010-25.

7. Roselli A, Khouri C, Rousit M, Blaise S, Cracowski JL. Safety profile of sclerosing agents: an analysis from the World Health Organization Pharmacovigilance Database VigiBase. Dermatol Surg 2019;45:1517-28.

8. Feied CF, Jackson JJ, Bren TS, Bond OB, Fernando CE, Young VC et al. Allergic reactions to polidocanol for vein sclerosis. Two case reports. J Dermatol Surg Oncol 1994;20:466-8.

9. Gupta C, Pandit RS, Jerath N, Narasimhan R. Severe life-threatening hypersensitivity reaction to polidocanol in a case of recurrent aneurysmal bone cyst. J Clin Orthop Trauma 2019;10:614-7.

10. Abbas M, Moussa M, Akel H. Type I Hypersensitivity Reaction. Treasure Island (FL): StatPearls; 2021. StatPearls Publishing Copyright © 2021. StatPearls Publishing LLC.

11. Bajwa SF, Mohammed RHA. Type II hypersensitivity reaction. Treasure Island (FL): StatPearls. 2021. StatPearls Publishing.
12. Szebeni J. Complement activation-related pseudoallergy: a new class of drug-induced acute immune toxicity. Toxicology 2005;216:106-21.
13. Jensen JT, Hanna C, Yao S, Micks E, Edelman A, Holden L, et al. Blockade of tubal patency following transcervical administration of polidocanol foam: initial studies in rhesus macaques. Contraception 2014;89:540-9.
14. Jensen JT, Hanna CB, Yao S, Mishler E, Chai D, Kiulia NM, et al. Polidocanol/doxycycline foam for nonsurgical permanent female contraception: 6 month data baboon contraception study. Fertil Steril 2019;112:e305-6.
15. Jensen JT, Hanna C, Yao S, Thompson E, Bauer C, Slayden OD. Transcervical administration of polidocanol foam prevents pregnancy in female baboons. Contraception 2016;94:527-33.
16. Jensen JT, Hanna C, Yao S, Bauer C, Morgan TK, Slayden OD. Characterization of tubal occlusion after transcervical polidocanol foam (PF) infusion in baboons. Contraception 2015;92:96-102.
17. Liu G, Crump M, Goss PE, Dancey J, Shepherd FA. Prospective comparison of the sclerosing agents doxycycline and bleomycin for the primary management of malignant pericardial effusion and cardiac tamponade. J Clin Oncol 1996;14:3141-7.
18. Sylvoz N, Villier C, Blaise S, Seinturier C, Mallaret M. [Polidocanol induced cardiotoxicity: a case report and review of the literature]. J Mal Vasc 2008;33:234-8.
19. Guide for the care and use of laboratory animals. 8th ed. Washington (DC): The National Academies Press. 2011.
20. Tessari L, Cavezza A, Frullini A. Preliminary experience with a new sclerosing foam in the treatment of varicose veins. Dermatol Surg 2001;27:58-60.
21. Bauer C. The baboon (Papio sp.) as a model for female reproduction studies. Contraception 2015;92:120-3.
22. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.e14.
23. Slayden OD, Lee DO, Yao S, Jensen JT. Polidocanol induced tubal occlusion in nonhuman primates: immunohistochemical detection of collagen I-V. Contraception 2016;94:521-6.
24. Indman PD, Brooks PC, Cooper JM, Loffer FD, Valle RF, Vancaillie TG. Complications of fluid overload from resectoscopic surgery. J Am Assoc Gynecol Laparosc 1998;5:63-7.
25. Fournier SB, D’Errico JN, Stapleton PA. Uterine vascular control pre-conception and during pregnancy. Compr Physiol 2021;11:1871-93.
26. Kramer JH, Weglicki WB. Inhibition of sarcolemmal Na+-K+-ATPase by palmitoyl carnitine: potentiation by propranolol. Am J Physiol 1985;248:H75-81.
27. Oexle B, Weirich J, Haverkampf K, Antoni H. Effects of polidocanol as a constituent of a venous sclerosing agent on cardiac electrical activity. Studies on the isolated perfused heart and papillary muscle of the guinea pig and on the isolated sinus node of the rabbit. Arzneimittel-Forschung 1988;38:1578-82.
28. Engelberger RP, Ney B, Clair M, Dabiri A, Alatri A, Mazzolai L, et al. Myocardial infarction after ultrasound guided foam sclerotherapy for varicose veins—a case report and review of the literature of a rare but serious adverse event. Vasa 2016;45:255-8.
29. Bernard PH, Lamouliatte H, Boulard A, Galperine I, Quinton A. [Reversible cardiac arrest after polidocanol endoscopic sclerotherapy of esophageal varices in infants]. Gastroenterol Clin Biol 1991;15:456-7.

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### Supplementary Table I. Mean arterial pressure (MAP) in baboons in response to transcervical pressurized administration of polidocanol/doxycycline foam (PDF), effect of dose

| MAP (% baseline) | Target dose = 200 mg polidocanol | Target dose = 400 mg polidocanol |
|------------------|----------------------------------|----------------------------------|
|                  | xxx85  | xxx88  | xxx89  | xxx90  | xxx87  | xxx92  | xxx93  | xxx94  | xxx96  |
| Delivered dose (mg) |        |        |        |        |        |        |        |        |        |
| 0                | 200    | 200    | 200    | 200    | 320    | 400    | 300    | 200    | 310    |
| 25               | 100    | 100    | 100    | 100    | 100    | 100    | 100    | 100    | 100    |
| 50               | 105<sup>a</sup> | 124    | 147    | 171    | 227    | 185<sup>b</sup> | 98    | 98    |
| 75               | 110<sup>a</sup> | 141    | 164    | 191    | 215    | 179    | 174    | 155    | 182    |
| 100              | 120<sup>a</sup> | 130    | 177    | 169    | 185    | 181    | 122    | 147    | 199    |
| 125              | 145<sup>a</sup> | 127    | 151    | 143    | 169    | 153    | 109    | 120    | 197    |
| 150              | 170<sup>a</sup> | 106    | 130    | 97     | 144    | 158    | 89     | 100    | 179    |
| 175              | 195<sup>a</sup> | 122    | 85     | 81     | 158    | 140    | 93     | 73     | 161    |
| 200              | 207    | 95     | 81     | 0<sup>b</sup> | 140    | 140    | 43     | 0<sup>b</sup> | 148    |
| 225              | 137    | 132    | 0<sup>b</sup> | c      | 154    |        |        |        |
| 250              | 112    | 125    | 0<sup>b</sup> | c      | 125    |        |        |        |
| 275              | 94     | 113    | 0<sup>b</sup> | c      | 110    |        |        |        |
| 300              | 98     | 113    | 0<sup>b</sup> | c      | 90     |        |        |        |
| 325              | 77     | 106    | c      | c      | 0<sup>b</sup> |        |        |        |
| 350              | 111    | c      | c      | c      |        |        |        |        |
| 375              | 96     | c      | c      | c      |        |        |        |        |
| 400              | 96     | c      | c      | c      |        |        |        |        |
| Post-treatment nadir | 117    | 59    | 64    | 41    | 67     | 94     | 0      | 0      | 42     |
| Post-treatment 35 min | 133    | 111    | 77    | 136    | 110    | 111    | 102    | 165    | 104    |

Female baboons received PDF: target dose 200 mg polidocanol (<i>n</i> = 4); target dose 400 mg polidocanol (<i>n</i> = 5). Although all four animals in the 200-mg group tolerated the full target dose, only one of five in the 400-mg group tolerated the full target dose, and two animals in this group required intervention (xxx93 received two doses of epinephrine while xxx94 received one dose). Data are presented as percent baseline.

<sup>a</sup>Owing to the infusion pump being set slightly faster than the target rate, some data points had to be extrapolated (xxx85 still received the target dose of 200 mg).

<sup>b</sup>Data missing owing to a loss of signal from monitoring equipment or blood pressure was presumed ‘0’ if it became nonpalpable.

<sup>c</sup>Administration of PDF stopped before reaching the target dose.
Supplementary Table II. Heart rate in baboons in response to transcervical pressurized administration of polidocanol/doxycycline foam (PDF)

| Heart rate (% baseline) | Target dose = 200 mg polidocanol | Target dose = 400 mg polidocanol |
|-------------------------|----------------------------------|----------------------------------|
|                         | xxx85 | xxx88 | xxx89 | xxx90 | xxx87 | xxx92 | xxx93 | xxx94 | xxx96 |
| Delivered dose (mg)     | 200   | 200   | 200   | 200   | 320   | 400   | 300   | 200   | 310   |
| 0                      | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   |
| 25                     | 99    | 103   | 106   | 102   | 109   | 98    | 104   | 97    | 101   |
| 50                     | 111a  | 114   | 123   | 108   | 113   | 129   | 133   | 111   | 107   |
| 75                     | 110   | 114   | 107   | 107   | 112   | 129   | 140   | 112   | 110   |
| 100                    | 112b  | 118   | 110   | 104   | 111   | 130   | 137   | 113   | 111   |
| 125                    | 117c  | 115   | 110   | 103   | 110   | 124   | 140   | 116   | 109   |
| 150                    | 121d  | 114   | 109   | 102   | 109   | 128   | 138   | 117   | 107   |
| 175                    | 122e  | 110   | 112   | 97    | 109   | 126   | 129   | 115   | 111   |
| 200                    | 121   | 111   | 107   | 96    | 111   | 127   | 116   | 106   | 111   |
| 225                    | —     | —     | —     | —     | 110   | 124   | b     | c     | 113   |
| 250                    | —     | —     | —     | —     | 109   | 122   | 109   | c     | 118   |
| 275                    | —     | —     | —     | —     | 109   | 119   | 113   | c     | 119   |
| 300                    | —     | —     | —     | —     | 109   | 119   | c     | c     | 114   |
| 325                    | —     | —     | —     | —     | 106   | 117   | c     | c     | c     |
| 350                    | —     | —     | —     | —     | c     | 117   | c     | c     | c     |
| 375                    | —     | —     | —     | —     | c     | 114   | c     | c     | c     |
| 400                    | —     | —     | —     | —     | c     | 114   | c     | c     | c     |
| Post-treatment nadir   | 100   | 91    | 98    | 85    | 99    | 105   | 101   | 97    | 95    |
| Post-treatment 35 min  | 103   | 91    | 98    | 88    | 99    | 108   | 132   | 99    | 95    |

Female baboons were administered PDF with four given a target dose of 200 mg polidocanol and five given a target dose of 400 mg polidocanol. All animals in the 200-mg group tolerated the full target dose. Only one of the five animals in the 400-mg group tolerated the full target dose, and two received epinephrine (xxx93, xxx94). Heart rate was not dramatically affected by PDF infusion. Data are presented as percent baseline.

*Owing to the infusion pump being set slightly faster than the target rate, some data points had to be extrapolated (xxx85 still received the target dose of 200 mg).

bData missing owing to loss of signal from monitoring equipment.

cAdministration of PDF stopped before reaching the target dose.
**Supplementary Table III.** Female baboons were administered polidocanol/doxycycline foam (PDF) with four given a target dose of 200 mg polidocanol and five given a target dose of 400 mg polidocanol

| O₂ sat (% baseline) | Target dose = 200 mg polidocanol | Target dose = 400 mg polidocanol |
|---------------------|-----------------------------------|----------------------------------|
|                     | xxx85 | xxx88 | xxx89 | xxx90 | xxx87 | xxx92 | xxx93 | xxx94 | xxx96 |
| Delivered dose (mg) |       |       |       |       |       |       |       |       |       |
| 0                   | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   |
| 25                  | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   |
| 50                  | 100    | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   |
| 75                  | 100    | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   |
| 100                 | 100    | 100   | 100   | 100   | 100   | 100   | 100   | 100   | 100   |
| 125                 | 100    | 100   | 100   | 99    | 100   | 99    | 100   | 100   | 100   |
| 150                 | 100    | 93    | 100   | 99    | 100   | 100   | 100   | 100   | 100   |
| 175                 | 100    | 100  | 100   | 99    | 100   | 100   | 100   | 100   | 100   |
| 200                 | 100   | 100  | 100   | 99    | 100   | 100   | 100   | 89    | 100   |
| 225                 |       |       |       |       | 100   | 100   | 100   | 100   | 100   |
| 250                 |       |       |       |       | 100   | 100   | 100   | 100   | 100   |
| 275                 |       |       |       |       | 100   | 100   | 100   | 100   | 100   |
| 300                 |       |       |       |       | 100   | 100   | 100   | 100   | 100   |
| 325                 |       |       |       |       | 100   | 100   | 100   | 100   | 100   |
| 350                 |       |       |       |       |       |       | 100   | 100   | 100   |
| 375                 |       |       |       |       |       |       | 100   | 100   | 100   |
| 400                 |       |       |       |       |       |       | 100   | 100   | 100   |
| Post-treatment nadir | 100   | 99    | 98    | 98    | 100   | 100   | 100   | 89    | 100   |
| Post-treatment 35 min | 100   | 99    | 99    | 98    | 100   | 100   | 100   | 99    | 100   |

All animals in the 200 mg group tolerated the full target dose. Only one of the five animals in the 400-mg group tolerated the full target dose, and two animals in this group required intervention (xxx93 received two doses of epinephrine while xxx94 received one dose). Data are presented as percent baseline.

*a* Owing to the infusion pump being set slightly faster than the target rate, some data points had to be extrapolated (xxx85 still received the target dose of 200 mg).

*b* Data missing owing to loss of signal from monitoring equipment.

*c* Administration of PDF stopped before reaching target dose.
**Supplementary Table IV.** Nonpressurized transcervical delivery of polidocanol foam (PF) and pressurized transcervical delivery of PF

| Nonpressurized cervical delivery | xxx16 | xxx17 | xxx19 | xxx20 | xxx22 |
|----------------------------------|-------|-------|-------|-------|-------|
| Polidocanol (mg)                 |       |       |       |       |       |
| Target                           | 400   | 400   | 400   | 400   | 400   |
| Delivered                        | 400   | 400   | 400   | 400   | 400   |
| Mean intrauterine pressure during PF infusion (mm Hg) | Missing<sup>a</sup> | 54 | 51 | 38 | 99 |
| >30% BP decrease?                | Y     | Y     | N     | N     | N     |
| Polidocanol (mg) at 30% decrease | 350<sup>b</sup> | 400 | n/a | n/a | n/a |
| Resolution                       | Rapid | Rapid | n/a | n/a | n/a |

| Pressurized transcervical delivery |       |       |       |       |       |
|-----------------------------------|-------|-------|-------|-------|-------|
| Polidocanol (mg)                  |       |       |       |       |       |
| Target                            | 400   | 400   | 400   | 400   | 400   |
| Delivered                         | 320   | 100   | 150   | 400   | 400   |
| Mean intrauterine pressure during PF infusion (mm Hg) | 692 | 103 | 196 | 265 | 153 |
| >30% BP decrease?                 | Y     | Y     | Y     | Y     | N     |
| Polidocanol (mg) at 30% decrease  | 320   | 100   | 150   | 350   | n/a   |
| Resolution                        | Slow  | Slow  | n/a   | Medium| n/a   |

BP, Blood pressure. N, no. Y, yes.

To administer PF without pressure, a Cook HSG catheter was inserted transcervically but without the balloon inflated. Two of five animals demonstrated a greater than 30% decrease from baseline in the mean arterial pressure (MAP), although both occurred near or following the completion of PF infusion and resolved rapidly without intervention.

To administer PF under pressure, a Cook HSG catheter was inserted transcervically with the balloon inflated. We observed a greater than 30% decrease in MAP from baseline during or after PF delivery in all five animals, with three animals requiring premature termination of PF infusion and experiencing a slow recovery from the induced hypotension.

<sup>a</sup>Intrauterine pressure was not recorded for this animal.

<sup>b</sup>We observed a 30% decrease in MAP after approximately 350 mg polidocanol was administered although she tolerated the entire target dose of 400 mg polidocanol.