

Case Study

Cranial Vena Cava Syndrome in Guinea Pigs with Chronic Jugular Vein Catheters

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Guinea pigs are a premier small animal model for infectious disease research, and chronic indwelling venous access ports may be used to facilitate various procedures. Here we report catheter-related lesions in 5 uninfected Dunkin–Hartley guinea pigs with chronic jugular vein catheters used for imaging studies. Three guinea pigs were found dead with no premonitory signs. At necropsy, there was severe bilateral pulmonary atelectasis due to 20 to 29 mL of pleural effusion resulting from catheter-related thrombosis and cranial vena cava syndrome. In addition, one of these 3 guinea pigs had a polymicrobial catheter infection with abscessation. A 4th clinically normal guinea pig was euthanized at the end of the study, having spontaneously lost its catheter 7 mo prior, and had 17 mL of pleural effusion. The 5th guinea pig was euthanized following pooling of contrast material around the distal catheter in the cranial vena cava on CT. By histology, affected animals had recent and remote thrombosis or fibrosis (or both) of the cranial vena cava and right atrial wall, with osseous and cartilaginous metaplasia. Cranial vena cava syndrome should be considered as a differential for dyspnea or death in chronically catheterized laboratory animals.

Abbreviations: FDG, 2-fluoro-2-deoxy-D-glucose; PET, positron emission tomography

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Guinea pigs are important research animal models, although their use has declined somewhat in recent years, in part due to limited reagent availability (for example, species-specific validated antibodies), only a single available inbred strain (13/N), and—until very recently—difficulty in creating genetic mutants. Despite these limitations, guinea pigs nonetheless remain a frequently used animal model for infectious disease studies, particularly because of their size, cost, and tractable nature.^{10,21} Guinea pigs are commonly used in filovirus research, including therapeutic agent development, because they develop histopathologic lesions and serum biochemical changes, including coagulopathies, similar to those observed in humans and NHP.^{5,27} Other key uses of guinea pigs as animal models of non-infectious research include for pathophysiology of the inner ear, osteoarthritis, asthma, and cardiac arrhythmias.^{13,23,26,32}

Chronic vascular cannulation of laboratory animals is a common technique to allow repetitive long-term vascular sampling (including invasive pressure measurements) and intravenous delivery of small molecules, imaging contrast agents and tracers, and other reagents.⁸ Functional obstruction or occlusion of the cranial vena cava (cranial vena cava syndrome) and chylothorax have previously been reported as an adverse consequence of central venous catheters and peripherally inserted central catheters in humans, rhesus macaques, and dogs.^{2,7,20,22}

Additional reported complications in laboratory animals have included physical trauma caused by the catheters (for example, perforation), infections, formation of bland (uninfected) or septic thromboemboli with or without infarction, and aneurysms and dissections.^{6,11,14,18,28}

Case Study

Eight SPF Dunkin–Hartley (CrI:HA, strain code 051) guinea pigs (*Cavia porcellus*; 4 sows and 4 boars; age, 40 d) with surgically implanted right jugular vein catheters were obtained from Charles River Laboratories (Wilmington, MA). The guinea pigs were acclimated to the Maximum Containment (BSL4) Laboratory at the United States NIH/National Institute of Allergy and Infectious Diseases, Division of Clinical Research, Integrated Research Facility at Fort Detrick. Animals were housed in IVC (One Cage, Lab Products, Seaford, DE) on paper bedding (TEK-Fresh 7099, Envigo, Madison, WI) and provided food and water without restriction. The water is treated by a reverse-osmosis system (RO8600, Edstrom Industries, Waterford, WI). All animals are fed a high-fiber guinea pig diet (Teklad 2041, Envigo). Environmental conditions were controlled, with a temperature setting of 72 °F (22.2 °C), humidity at 50%, and a 12:12-h light:dark cycle. MR-compatible miniature vascular access ports (PinPorts, Instech Laboratories, Plymouth Meeting, PA) were attached to the external portion of the catheter for catheter maintenance and venous access. Catheters were flushed weekly with heparinized saline (10 U/mL) and locked with heparinized glycerol (500 U/mL). All work was conducted in a Maximum Containment (BSL4) Laboratory at the Integrated Research

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Table 1. Animal demographics and pathologic findings

Animal	Disposition, duration of catheterization	Sex	Pleural effusion	Pulmonary atelectasis	Other gross findings	Thrombosis	Mural remodeling in right atrium and cranial vena cava	Other histologic findings
1	Found dead, 151 d	M	>27 mL, blood-tinged, chylous	Yes	Postmortem intestinal rupture	Cranial vena cava, subacute	Yes	Mild to moderate pulmonary edema
2	Found dead, 184 d	M	>29 mL, blood-tinged, chylous	Yes	None	Catheter sheath	Yes	Moderate pulmonary edema
3	Found dead, 244 d	F	>20 mL, blood-tinged, serous	Yes	>1.5 mL, blood-tinged, serous pericardial effusion	No	Yes	Jugular and cranial vena caval phlebitis and mural abscess with bacteria; thromboemboli in lungs; tricuspid valve normal
4	Euthanized due to cranial vena cava thrombosis (CT imaging), 198 d	F	None	No	None	Right atrium and jugular, chronic	Yes	Chronic sublingual sialoadenitis
5	Euthanized at end of study, 381 d	F	None	No	None	No	Yes	None
6	Euthanized at end of study, 381 d	M	None	No	None	No	Yes	None
7	Euthanized at end of study, 262 d ^a	M	>17 mL, blood-tinged, serous	Yes	None	No	Yes	None
8	Euthanized at end of study, 169 d ^b	F	None	No	None	Yes	No	None

^aCatheter was spontaneously removed at approximately 7 mo prior to death.

^bCatheter was spontaneously removed at approximately 10 mo prior to death.

Facility at Fort Detrick that is fully AAALAC-accredited. All animal experiments were performed in accordance with animal study protocols approved by the Division of Clinical Research Animal Care and Use Committee. Protocols were compliant with the US Department of Agriculture Animal Welfare Act regulations¹ and adhered to the recommendations stated in the *Guide for the Care and Use of Laboratory Animals*.¹²

Guinea pigs were used for imaging development studies including positron emission tomography (PET) and CT.⁵ For imaging, guinea pigs were anesthetized with isoflurane (Patterson Veterinary, Greeley, CO) 1% to 4% in grade D breathing air in an anesthesia chamber and then by mask and a calibrated vaporizer. Contrast agents included Isovue-300 (Bracco Diagnostics, Monroe, NJ) for CT imaging and 2-fluoro-2-deoxy-D-glucose (¹⁸F-FDG; Cardinal Health, Dublin, OH) for PET imaging. Imaging agents were administered by IV infusion. Isovue-300 (2 mL/kg) was administered through intravenous infusion by using the miniature access ports. [¹⁸F]FDG was administered in a subset of 5 animals (guinea pigs 3 through 6 and 8) to optimize PET and CT imaging techniques for future studies in this species and to compare kinetics between intravenous and intramuscular uptake of the radiotracer.

Gross pathology. Three guinea pigs (2 boars and one sow) were found dead with no premonitory signs (animals 1 through

3; Table 1). All 3 had obvious caudal bulging of the diaphragm into the abdominal cavity. The 2 boars each had 27 mL or 29 mL or more of blood-tinged, milky, turbid (chylous) pleural effusion (Figure 1 A through C). The sow had more than 20 mL of blood-tinged, turbid, serous pleural effusion, with more than 1.5 mL of pericardial effusion. All 3 of these animals had marked and diffuse pulmonary atelectasis (Figure 1 D), although the lungs still floated in formalin. Guinea pig 3 had obvious fibrin deposition, hyperemia, and thickening of the wall of the jugular and cranial vena cava around the catheter.

In addition, another sow (no. 4) was euthanized after a fibrinous catheter sheath was identified due to contrast pooling in the cranial vena cava on CT imaging. This animal lacked grossly evident lesions, but gross dissection of the right jugular vein, cranial vena cava, and right atrium was limited. A 3rd boar (animal no. 7) was euthanized at the end of the study, with no clinical abnormalities noted. This guinea pig had spontaneously lost or removed its catheter approximately 7 mo prior to necropsy and consequently was shifted to a training protocol. At necropsy there was more than 17 mL of blood-tinged, turbid, serous pleural effusion with pulmonary atelectasis. The remaining 3 guinea pigs were euthanized at the end of the study; there were no gross abnormalities. One of these animals (no. 8) had spontaneously lost or removed her catheter approximately

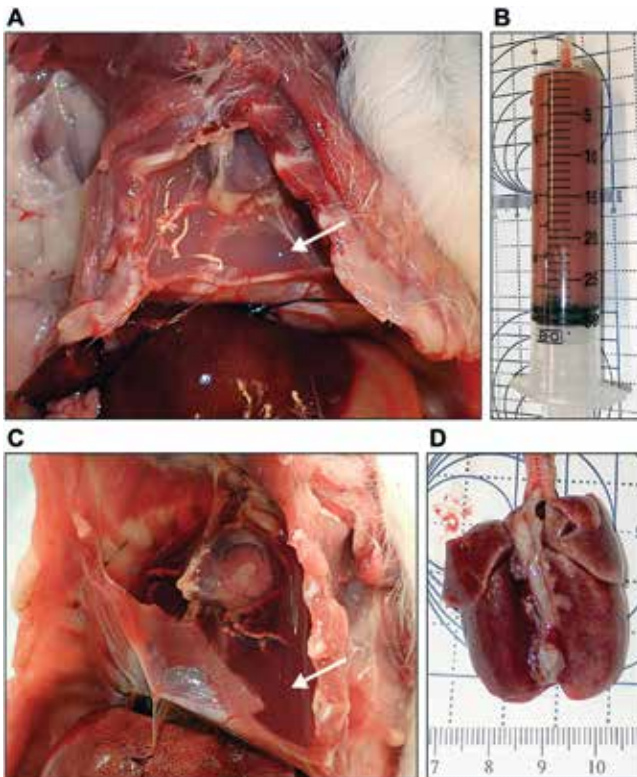


Figure 1. (A and B) Guinea pig 1. There is more than 27 mL of chylous effusion filling the pleural spaces and obscuring the heart and lungs (A, arrow). (B) Syringe shows the volume and chylous nature of the effusion. (C and D). Guinea pig 2. There is more than 29 mL of chylous pleural effusion (C, arrow) with severe and diffuse atelectasis of the lungs (D).

10 mo prior. No facial swelling or edema was noted in any of the animals. Fluid analyses of effusions, including specific gravity and cytology, were not practical within the BSL4 facility, due to the absence of appropriate equipment within containment and the requirement to irradiate unfixed specimens prior to removal from containment. Bacterial cultures were impractical in animals with pleural effusions that were found dead and had significant autolysis; one of these animals had postmortem intestinal rupture.

Tissues were fixed for 72 h in 10% neutral buffered formalin before automated processing (Tissue-Tek VIP-6, Sakura Finetek USA, Torrance, CA) followed by paraffin embedding (Tissue-Tek model TEC, Sakura). Samples for slides were cut at 4 μ m on a microtome (model 2245, Leica), stained with hematoxylin and eosin, and coverslipped. Additional slides were stained with Brown and Brenn Gram stain and Masson trichrome stain. Gross necropsies and slide examinations were performed by a single board-certified veterinary pathologist (ACVP diplomate). All images were captured by using a microscope (model DM3000, Leica Microsystems, Buffalo Grove, IL), digital camera (model DFC 500, Leica) and Application Suite version 4.10.0 (Leica).

Histopathologic findings. A large nonadherent acute fibrin thrombus was present in the cranial vena cava of guinea pig 1, filling approximately 60% of the luminal cross-sectional area (Figure 2 A and B). A fibrin catheter sheath was present in the cranial vena cava of guinea pig 2.¹⁹ Guinea pig 3 had chronic-active suppurative phlebitis of the right jugular vein and cranial vena cava, with a focally extensive mural abscess containing gram-negative rods and gram-positive cocci. Guinea pig 4 had 2 nonocclusive, mature, organized thrombi in the

jugular vein and cranial vena cava. For all animals except no. 8 there was extensive remodeling of the right atrial wall, including mature endocardial and myocardial fibrosis (which was occasionally transmural), endocardial hyperplasia, and well-differentiated myocardial nodules of hyaline cartilage and bone with marrow elements (cartilaginous and osseous metaplasia). Mural remodeling, including abundant mature medial fibrosis (Figure 2 C and D) extended into the cranial vena cava in all guinea pigs except no. 8 (Figure 2 E and F); guinea pig no. 8 was normal except for a small, organized, mural thrombus at the atriocaval junction. In addition, 6 of the 7 animals with chest imaging demonstrated calcification in the area of the distal cranial vena cava or right atrium on CT (Figure 3 A through C). Pulmonary thromboemboli were present in a single animal (no. 3) only; this animal had concurrent bacterial thrombophlebitis and abscessation. In another animal (no. 4), a single medium pulmonary artery was effaced by granulomatous inflammation with foreign material (embolized hairshafts). None of the animals had any evidence of sup-puration or neutrophilic inflammation of the visceral pleura consistent with bacterial infection of the pleural space.

Discussion

Cranial (superior) vena cava syndrome results from the obstruction, stenosis, or occlusion of the cranial vena cava through various processes, including thrombosis and neoplasia.^{22,24} Pleural effusions may occur in a significant proportion of patients, because increased venous hydrostatic pressure is thought to restrict pleural lymphatic drainage, thus resulting in fluid accumulation.^{7,24,25,30} In addition, direct or indirect damage to the thoracic duct may occur. Other typical features of cranial vena cava syndrome can include edema of the face and neck, dyspnea, and dilated collateral veins of the thorax. Surgical ligation of the cranial vena cava has been described as an experimental animal model of superior vena cava syndrome in dogs.³ In those studies, initial pleural effusions were bloody and nonchylous, with later development of chylous and bloody effusions in approximately half of the animals, with frequent death from respiratory embarrassment within several weeks. In the present study, occlusion or stenosis of the cranial vena cava due to acute thrombosis or chronic mural fibrosis (or both) were thought to impair thoracic lymphatic drainage in 4 guinea pigs, leading to significant pleural effusions that were fatal in 3 animals. Caval syndrome associated with fibrosis of intravenous pacemaker leads has been previously described in people and in dogs.^{15,29} Due to the relatively sedentary nature of guinea pigs, combined with the inability to auscultate animals in a BSL4 environment,¹⁶ premonitory clinical signs of disease were not observed. No pleural effusions were identified by PET or CT; however, none of the animals with catheters that died were imaged within 46 d of death, and the boar with pleural effusion that had spontaneously lost its catheter had not been imaged for 287 d. Animals were imaged a variable number of times, ranging from only once (CT with contrast only, guinea pigs 1 and 2, at 126 and 159 d before necropsy, respectively) to 10 times over the course of 1 y (PET-CT and CT with contrast, guinea pig 5). Although we cannot exclude the possibility that imaging contrast agent or radiotracer may have contributed to lesion development, both agents are widely used in human medicine and generally considered safe.

The histology of the jugular vein, cranial vena cava and right atrium in animals with long-term venous catheters has been described previously in other species and is largely consistent with

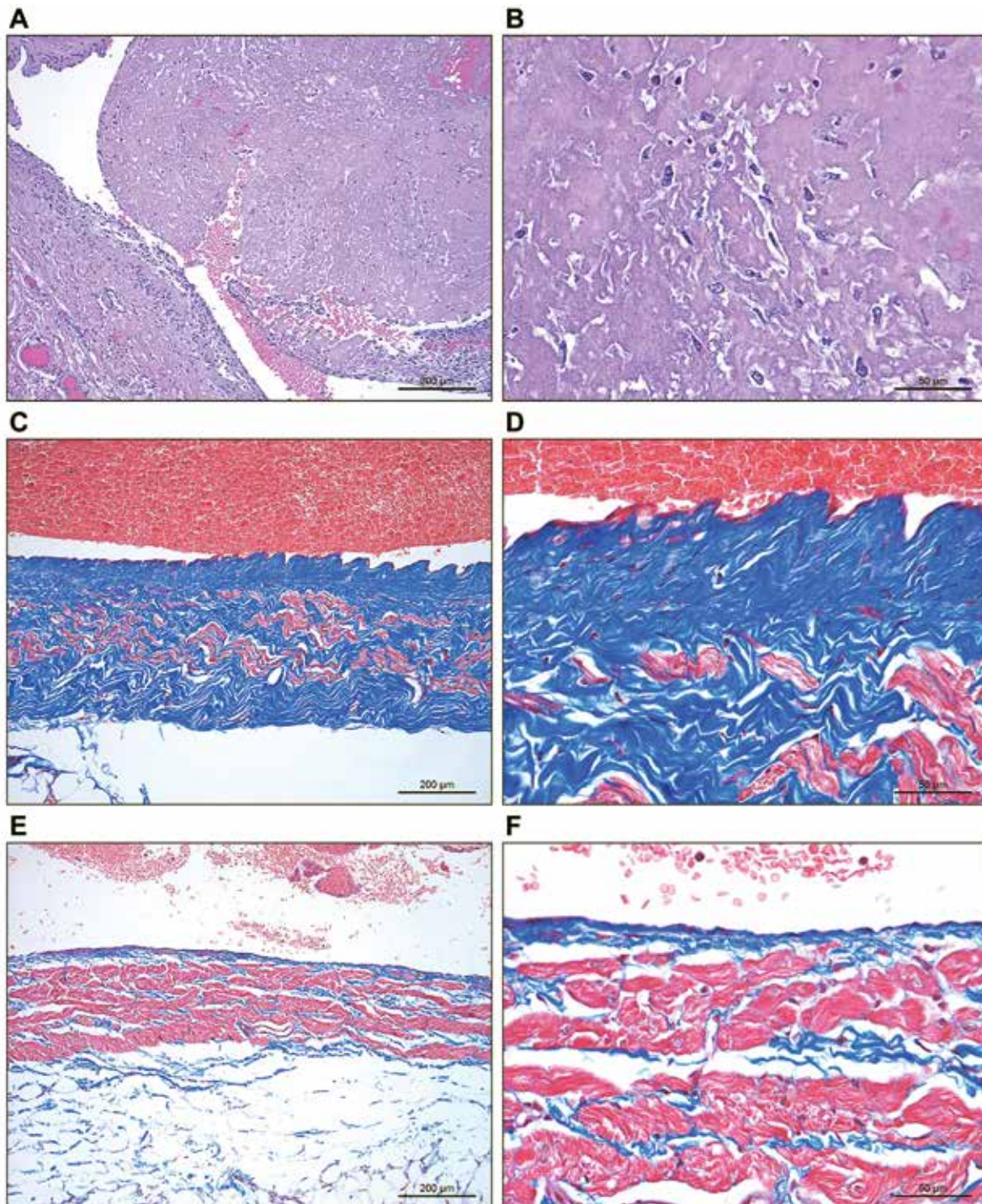


Figure 2. (A and B) Guinea pig 1. A large, nonadherent thrombus with nascent reendothelialization and organization fills the cranial vena cava. The vein wall is at the lower left in panel A. (B) A higher-magnification image shows the nonseptic fibrinous nature of the thrombus with ingrowth of fibroblasts and macrophages. (C and D) Guinea pig 7. Diffuse mature, mural fibrosis (blue) expands and replaces the wall of the cranial vena cava. Masson trichrome stain. (E and F) Guinea pig 8. Normal cranial vena cava with tunica media composed of bundles of smooth muscle (red) with scant intervening collagen (blue). Masson trichrome stain.

what was observed in these animals.^{14,18,31} Lesions of the right atrium and cranial vena cava were minimal in the sow that had lost her catheter after only 4 mo on the study (approximately 1 y before euthanasia). The frequent presence of cartilaginous and osseous metaplasia in the right atrium is likely a unique feature of guinea pigs, a species in which similar metaplasia is common in the lung and ciliary body.^{9,17} Unilateral chronic inflammation and atrophy of the sublingual salivary gland was present in

a single sow (no. 4) but has been observed in other catheterized guinea pigs at this institution (data not shown) and is interpreted as a complication of surgery. The presence of ectatic salivary ducts in some animals is consistent with inadvertent ligation at the time of catheter placement.

Overall, jugular vein cannulation was reasonably well tolerated, with no adverse events observed until the animals had been on study for approximately 5 mo and only a single catheter

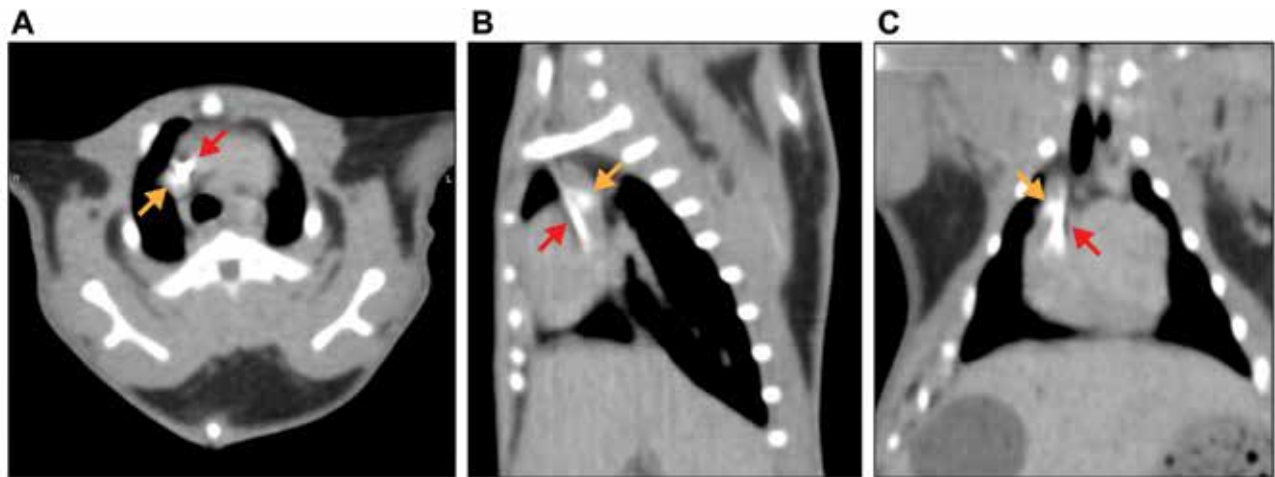


Figure 3. (A) Axial, (B) sagittal, and (C) dorsoventral postcontrast CT images from guinea pig no. 3 at 25 d after catheter implantation, showing calcification in the right atrium–cranial vena cava junction (orange arrows) and collection of contrast material in the cranial vena cava, indicating a fibrinous sheath around the distal end of the catheter tip (red arrows).

infection. Cranial vena cava syndrome causing pleural effusion and respiratory embarrassment should be considered in any laboratory animal with a central venous catheter displaying dyspnea or found dead, even if the catheter was previously removed.

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