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Acute Bacterial Endocarditis in Dogs After Constriction of the Inferior Vena Cava and Ligation of the Thoracic Duct

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Acute bacterial endocarditis in dogs is relatively rare. In a previous study we demonstrated that surgically produced impairment of cardiac lymph flow predisposed to the development of acute bacterial endocarditis after the intravenous injection of suspensions of staphylococci (1). More recently we have observed the development of endocarditis in dogs in which no bacteria were injected, but in which the thoracic duct lymph flow was obstructed and the inferior vena cava had been constricted in its thoracic portion. We believe that these observations may define additional factors important in the pathogenesis of valvular endocarditis.

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Methods

Twenty-three dogs were operated upon to constrict the inferior vena cava and to resect a segment of the thoracic duct. The chest was opened under aseptic conditions through an incision in the 4th or 5th left intercostal space. A cotton ligature was used to constrict the inferior vena cava approximately 50 per cent at a site above the diaphragm, and a 2.5 cm long segment of the thoracic duct in the area of the upper left mediastinum was resected between cotton ligatures. The dogs were ventilated during the operation by means of a Harvard respirator. In all of the animals a wedge biopsy of the liver was obtained through a small abdominal incision before opening the chest. The specimen was fixed immediately in 10% formaldehyde solution. Postoperatively each dog was given procaine penicillin, 400,000 units intramuscularly daily for 4 days. Venous pressures were obtained with a saline manometer connected to a length of polythene tubing that had been threaded into the femoral vein.

Those animals that did not die spontaneously were killed with intravenous sodium pentobarbital between 15 and 62 days after operation and specimens for histological study were obtained from the heart, lungs and liver. The experiments originally were designed to study the effects on the liver of mechanically induced impairment of hepatic venous and lymph drainage. The development of acute bacterial endocarditis was an unexpected finding. It was for this reason that blood or tissue cultures for identification of the causative organisms were not obtained.

In 6 dogs examination at autopsy revealed that the ligature around the inferior cava had slipped, and that no constriction was then present. These dogs have been used as controls.

Results

Nine of the 17 dogs with inferior vena cava constriction and obstruction to thoracic duct lymph flow developed an acute endocarditis (Table 1). In 7 dogs the lesion was on the mitral valve, it was on the aortic valve in one dog, and on the right ventricular endocardium in one dog. In the dog with aortic valve infection, the lesion was severe and ulcerating; in the animals with mitral valve involvement, the lesions varied from inflammation without vegetations to ulcerating vegetative disease (Figs. 1 and 2). Gram stains of the involved valves revealed large numbers of gram-positive cocci. By morphological criteria they were most likely streptococci, forming large clumps and/or a fine dispersion throughout the valves (Fig. 3). Occasionally cocci were also seen within dilated, endothelium-lined vascular channels that we considered to be lymphatics. Acute myocarditis with abscess formation was present in two of the dogs that developed ulcerating lesions of the mitral valve.

Table 1 The Occurrence of Endocarditis in Dogs with Thoracic Duct Ligation with and without Inferior Caval Constriction

	Total Number of Dogs	Number with Endocarditis	Number with Myocarditis and Abscess Formation	Number with Associated Lung Pathology
Thoracic duct ligation without inferior vena cava constriction	6	1	0	3
Thoracic duct ligation and constriction of the inferior vena cava	17	9	2	7

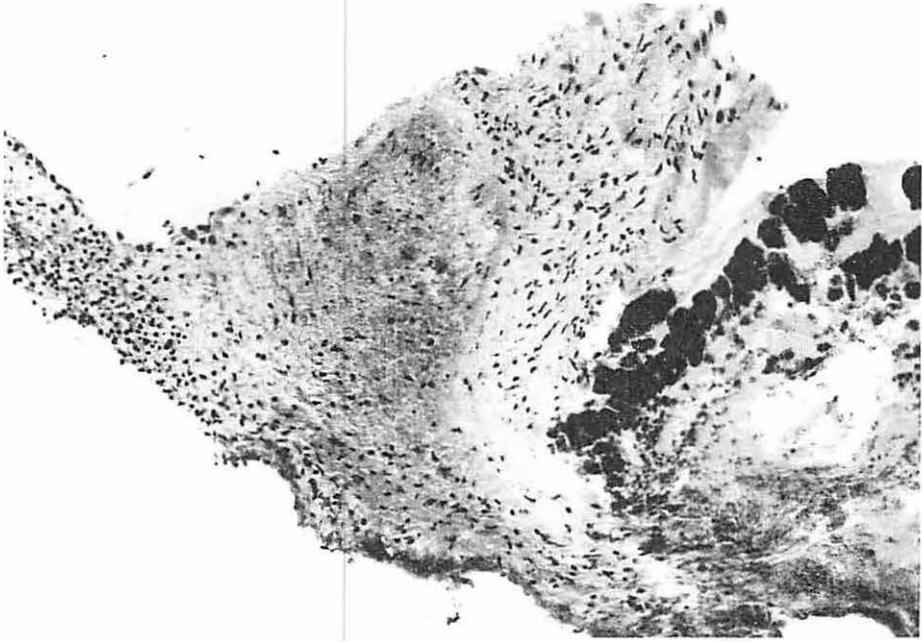


Fig. 1 Dog No. 894; 28 days after operation. Mitral valve. Vegetative endocarditis with ulceration. The black areas are clumps of bacteria. Hematoxylin and eosin X 220.

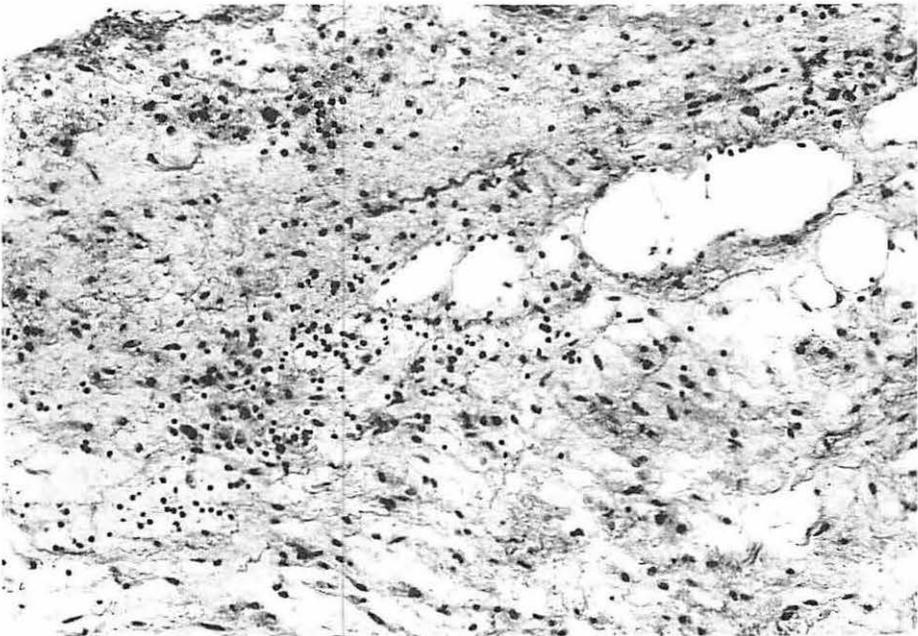


Fig. 2 Dog No. 5340; 45 days after operation. Mitral Valve. There is pronounced cellular infiltration. The distended vascular channels are considered to be lymphatics. Hematoxylin and eosin X 220.

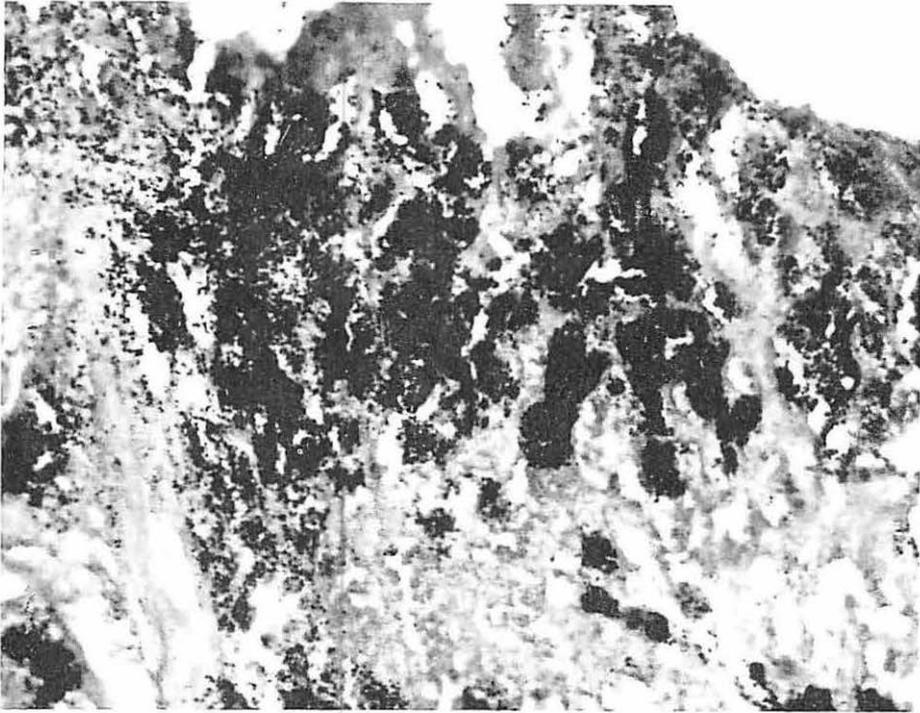


Fig. 3 Dog No. 4840; 20 days after operation. Mitral valve. Gram stain. Gram-positive cocci (black) x 750.

Fourteen of the total of 23 dogs died between 5 and 48 days after operation and 10 of them showed evidence at autopsy of pneumonia, pulmonary abscess formation or pulmonary infarction; six of these 14 were in the group that developed valvular endocarditis. The remaining 9 dogs were killed at varying times after operation.

Pneumonia occurred in 7 of the 17 animals with inferior vena cava constriction. In 4 of the 7, lung abscess formation was also present. In 8 of the 17 dogs thrombus formation distal to the site of constriction of the inferior vena cava was found at autopsy; in 3 of these 8 dogs pulmonary emboli were also found. In 3 other animals pulmonary emboli were present without evidence of thrombus formation in the inferior vena cava. A statistically significant correlation could not be defined between the occurrence of pneumonia or pulmonary emboli and the presence of valvular endocarditis. None of the animals showed evidence of inflammation or infection of the tricuspid or pulmonary valves.

One of the dogs in which the inferior vena cava ligature was found to be loose at post-mortem examination developed an endocarditis of the mitral valve. This animal, as well as two others from this group of six, also had pneumonia with lung abscess formation seen at postmortem examination.

Venous pressure measurements from below the inferior vena cava constriction were obtained in 15 of the dogs from one to four times after operation. Pressures taken soon after operation varied between 16 and 25 cm of water, and tended to fall to or towards normal

with the passage of time. There was no correlation between the magnitude of venous pressure obtained either immediately after operation or close to the time of death and the subsequent finding of endocarditis. Similarly, the occurrence of endocarditis was not related to the time and frequency of various pressure determinations. Twelve dogs had ascites at postmortem examination; 3 of these were in the group that had endocarditis. All of the control liver biopsies were normal except in 4 dogs. These latter animals, 2 of which subsequently developed endocarditis (and one of which was in the control group), showed either fatty infiltration, small granulomata, round cell infiltration, or mild portal fibrosis. All the dogs with inferior vena cava constriction showed hepatic abnormalities in the post-mortem histologic studies. The pathology consistently included central venous congestion; many of the animals also showed areas of liver necrosis and had increased hepatic fibrosis. The extent of liver pathology bore no correlation to the occurrence of valvular endocarditis.

Discussion

Valvular endocarditis, unusual in our laboratories in routine autopsies performed over many years, occurred in over one-half of the dogs with constriction of the inferior cava and obstruction to thoracic duct lymph flow. We do not know why the endocarditis occurred, but report the data because of its unusual nature. The experiments are admittedly incomplete, and as has been noted, were originally designed as part of another project. The unusual observations in these dogs were threefold: (a) the occurrence of left-sided valvular infective endocarditis in dogs with partial obstruction to the inferior vena cava above the diaphragm and with obstruction to thoracic duct lymph drainage (b) the frequent occurrence of pulmonary infarction, pulmonary abscesses and pneumonia, and (c) the frequent thrombus formation distal to the inferior vena cava ligature site. It appears reasonable to hypothesize that these three phenomena were related to each other. It is possible that infected thrombi occurring at and below the sites of caval ligature gave rise to pulmonary emboli, and that the former were due to poor surgical antisepsis. Though we doubt this explanation, even if true the occurrence of endocarditis in the dog under these circumstances remains unusual and noteworthy.

Infective valvular endocarditis, recently reported as occurring with increasing frequency on normal heart valves (2), remains a major clinical problem. Though we have learned more about the mechanisms of its occurrence, many factors in host resistance remain an enigma. In this series of experiments we are posed the question of how marked inferior caval obstruction and thoracic duct occlusion predisposed to the frequent occurrence of infective endocarditis.

Effects of ligating the thoracic duct on host resistance to infection

No increased frequency of bacterial endocarditis has been reported in the many studies on the effects of ligation of the thoracic duct (3, 4, 5), and consequently it is unlikely that this intervention alone can explain our findings. We have previously obstructed the thoracic duct and markedly narrowed the superior vena cava, and in these experiments there was no evidence of endocarditis or thrombus formation at the ligature site (6). However, *Drinker* and *Field* (7) alluded to a problem of infection with thoracic duct ligation studies: "The problem of nutritional disturbances and survival after excluding the lymph from the circulation seems never to have been attacked with much success, not because the thoracic duct has not been tied but because failure to tie the entrances on the right side or else the onset of infection have vitiated the results." It is known that lymphocytes

(8) and eosinophils (3) fall markedly after thoracic duct ligation. *Lee* (8) found that the lymphocytes returned to control levels in cats at about 3 weeks after the thoracic duct had been obstructed, and concluded that by this time there was an adequate collateral vessel development. There is some evidence that interference with lymph flow from a bodily part predisposes that part to infection and inflammation (9, 1). Thus, it can be stated that ligation of the thoracic duct in the dog may predispose the animal to infection in certain ways.

Effects of obstruction of the inferior vena cava above the diaphragm

Ligation of the inferior vena cava above the diaphragm frequently results in ascites, with hepatic and intestinal venous stasis, and marked increases in lymph flow (10). Thoracic duct lymph flow has been shown to be markedly increased in *Laennec's* cirrhosis in man (11). Among the predisposing factors to infective endocarditis in man stressed by *Buchbinder* and *Roberts* (2) was alcoholism. In their report they made no attempt to explain why alcohol seemed to play this important role in decreasing host defense mechanisms, but it is possible that it was via an action on the liver.

In man with obstruction of the inferior cava due to thrombus formation related to sepsis, recurrent pulmonary emboli and pulmonary abscesses were found to be frequent (12). *Missal* and his co-workers (13) emphasized that pulmonary embolism should alert the clinician to the possibility of thrombosis in the inferior vena cava. We have been able to find one patient reported with thrombosis of the inferior vena cava who at postmortem examination was found to have an endocarditis of the aortic valve (14). It would appear that interference with inferior vena caval blood flow may directly, via venous stasis in the liver and bowel, and indirectly, via lymph overload on the thoracic duct system with resultant relative lymph stasis (15), play a role in determining host resistance to infection.

The experimental design in the experiments being reported clearly included a number of factors which would affect host resistance to infection, and these have been summarized. We are unable to define which of the various factors might have been the most important. We are left with the question of the origin of infected thrombi below the caval ligation. The possibilities include bacterial contamination from the intestine, with increased permeability due to venous blood and lymph stasis, and introduction of bacteria by the surgical procedures or by the repeated determinations of venous pressures.

Irrespective of the mode of entry of the bacteria, the frequent occurrence of pulmonary infection was undoubtedly at least in good part due to the occurrence of septic emboli to the lung. *Roberts* and *Buchbinder* (16) have stressed the frequency of pneumonia and pulmonary abscess in their patients with right-sided valvular endocarditis as being a result of septic emboli from the right-sided heart lesions. In 6 of the 12 patients they studied at least one left-sided valve was also infected, and these authors emphasize that the infection on the left was probably secondary to infection on the right from septic pulmonary emboli. Our results in the dog have certain interesting counterparts to their important study, but it would appear that in the dog the right-sided valves are more resistant to infection than in man. We have had a similar experience after injecting virulent staphylococci intravenously in cardiac lymph-obstructed dogs (1).

Through our report provides no definitive explanation for the occurrence of left-sided bacterial endocarditis in dogs with thoracic duct occlusion and interference with inferior vena cava flow, we can reasonably conclude that the resistance to infection in these animals was lowered and that the endocarditis followed septic embolization to the lung. Septic pul-

monary emboli and pneumonia may represent important predisposing factors to left-sided infective endocarditis, an observation which may have clinical counterparts in man.

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