The Journal of Veterinary Medical Science

NOTE

Internal Medicine

Clinical and postmortem findings of pentalogy of Fallot in an 18-month-old Holstein heifer

Dai ISHIYAMA[1)], Eiji MAKINO[1)], Yoshihiro NAKAMURA[1)], Makoto UCHIDA[1)], Yukio ONODERA[1)], James K. CHAMBERS[2)], Kazuyuki UCHIDA[2)] and Fuko MATSUDA[2)]*

[1)]Sekiyado Branch Office, Western Veterinary Clinical Center, Chiba Prefectural Federated Agricultural Mutual Aid Association, 462-11 Kirigasaku, Noda-shi, Chiba 270-0213, Japan
[2)]Department of Veterinary Medical Sciences, Graduate School of Agriculture and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

J. Vet. Med. Sci.
81(11): 1676–1679, 2019
doi: 10.1292/jvms.19-0147

Received: 14 March 2019
Accepted: 12 September 2019
Advanced Epub:
1 October 2019

ABSTRACT. An 18-month-old female Holstein Friesian heifer presented with a history of stunted growth and a recent onset of anorexia; she presented with cyanosis and eventually died. A postmortem examination revealed obstruction of the right ventricular outflow tract, ventricular septal defect, overriding aortic root, right ventricular hypertrophy, and an atrial septal defect, indicating a pentalogy of Fallot (POF). In addition to POF, the heifer also had pulmonary artery dilatation, although she did not present with patent ductus arteriosus. This heifer had the longest lifespan among the Holstein cattle reported to have POF, which may be secondary to delayed pulmonary obstruction due to deformation of one of the pulmonary valves.

KEY WORDS: congenital heart disease, Holstein Friesian heifer, pentalogy of Fallot, postmortem examination

Pentalogy of Fallot (POF) is a rare form of cyanotic congenital heart disease and is characterized by Tetralogy of Fallot (TOF) with either an atrial septal defect (ASD) or a patent foramen ovale (PFO). TOF, which is characterized by stenosis of the right ventricular outflow tract, ventricular septal defect (VSD), overriding aortic root, and right ventricular hypertrophy [33, 38], is reported in 34 of 100,000 live human births and accounts for 8–10% of congenital heart disease [35]. The prevalence of congenital heart diseases in bovine fetuses collected at abattoirs is 0.7% [15] and TOF accounts for 7.5% of these cases [12]. POF has been reported in many species, including cattle [4, 6, 8, 9, 12, 21], a ram [27], a Bengal Tiger [26], a Siberian Tiger [31], and a Korean Sapsaree dog [25], as well as in human patients [1, 2]. General symptoms of POF are similar to that of TOF, including exercise intolerance, cyanosis, tachycardia, murmur, and tachypnea [8, 9, 21].

Currently, 23 cases of TOF or POF have been reported in cattle. Out of the 23, 5 cattle (3 cases of Holsteins between 11 days and 7 months old [4, 21], a 2-and-a-half-year-old Guernsey [6], and an 8-month-old Japanese Black [12]) have been reported thus far as cases of POF. We excluded 2 cases of TOF accompanied by PFO in Fisher's reports from the POF cases, because whose PFO was reported to be anatomically patent but functionally competent [8, 9]. Among the 5 POF cases, 2 cattle are reported to have pulmonary artery dilatation [4, 6] and 2 cattle are reported to have patent ductus arteriosus (PDA) [12]. We report a case of an 18-month-old Holstein heifer that died from POF, which had a longer lifespan than 3 other Holsteins reported to have had POF.

An 18-month-old female Holstein Friesian heifer, which was born on Dec 13th in 2014, presented with a history of stunted growth and acute anorexia at a tie-stall dairy farm in Ibaraki, Japan. Heifers at this farm usually experience heat around 12 months of age, but this animal was first in heat and artificially inseminated at the age of 17 months. On day 1 of treatment, elevated rectal temperature (41.4°C), tachycardia (104 beats/min), and tachypnea (60 breaths/min) were observed. A murmur could not be auscultated, most likely due to the sound of electric fans and the expiratory lung noises caused by tachypnea. Based on the high rectal temperature and tachypnea, the animal was initially diagnosed with bacterial pneumonia and treated with antibiotics including a streptomycin/penicillin mixture, enrofloxacin, florfenicol, and oxytetracycline as well as non-steroidal anti-inflammatory drugs from day 1 to day 14, but the clinical symptoms did not improve. On day 15, a holosystolic heart murmur, bilateral distension of the external jugular veins, and cyanosis were seen in addition to fever (39.8°C), tachycardia (96 beats/min), and tachypnea (48 breaths/min). There was no evidence of submandibular edema. A complete blood cell count and blood

*Correspondence to: Matsuda, F.: afukomat@mail.ecc.u-tokyo.ac.jp

biochemistry on day 15 revealed a mild leukocytosis (12.8 × 10^3 /μl), while red blood cells (7.99 × 10^6 /μl), hematocrit (32.1%), hemoglobin concentration (11.6 g/dl), protein concentration (7.2 g/dl), and albumin concentration (2.7 g/dl) were in the normal ranges. Electrophoretogram of the serum proteins was not indicative of hyperglobulinemia. Based on these findings, the existence of cardiovascular disease was suspected, in addition to pneumonia. Due to the poor prognosis of cardiovascular disease and unchanged systemic condition, no further treatments were performed.

The animal died on day 21 (July 4th, 2016), at the age of 18 months and 21 days, and a thoracic necropsy was performed. The heart was severely enlarged and adhered to the pleura. The lungs were extensively congested, and pneumonia was present, whereas subcutaneous edema, pleural effusion, and pericardial effusion were not. The heart was removed and fixed with 8% formaldehyde (Mildform; FUJIFILM Wako Pure Chemical Corp., Osaka, Japan). Dissection of the heart revealed obstruction of the right ventricular outflow tract (Fig. 1A), VSD (Fig. 1B), overriding aortic root, right ventricular hypertrophy (Fig. 1C), and ASD (Fig. 1D). Deformation of one of the pulmonary valves and dilatation of the pulmonary artery to a diameter of approximately 7 cm were also observed (Fig. 1A). The VSD was present in the membranous part of the ventricular septum with a diameter of approximately 2.5 cm (Fig. 1B). The right ventricular wall was thickened, with a thickness ratio of the left and right wall of approximately 1:1, while the normal ratio is 3:1 (Fig. 1C). PDA was not observed, indicating that the pulmonary artery was the only pathway leading to the lungs. The postmortem findings confirmed the diagnosis of POF with pulmonary artery dilatation and without PDA (Fig. 2). It was not clear from the postmortem examination whether these findings were primary or secondary defects.

Here we report a case of a deceased 18-month-old Holstein heifer with POF which included pulmonary artery dilatation but not

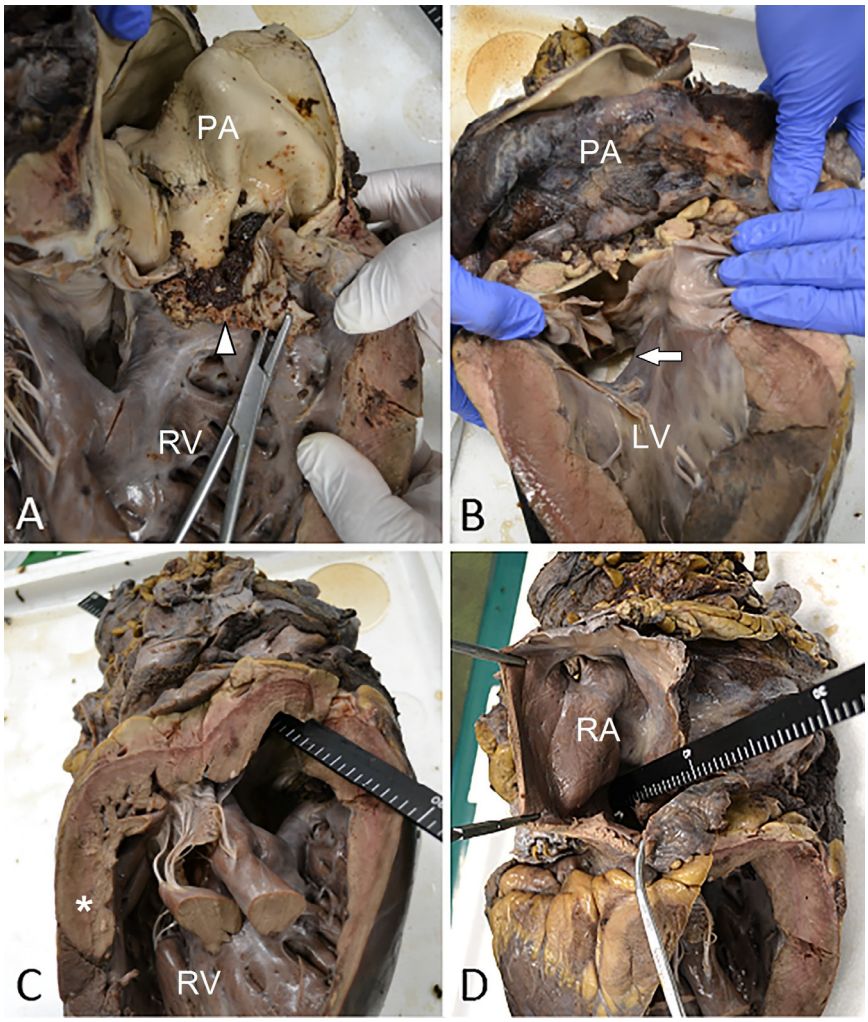

Fig. 1. Pathological findings of pentalogy of Fallot in a 19-month-old Holstein heifer. Dissection of the heart revealed obstruction of the right ventricular outflow tract (A), a ventricular septal defect (B), overriding aortic root, right ventricular hypertrophy (C), and an atrial septal defect (D). Obstruction of the right ventricular outflow tract was likely caused by clots that formed at the pulmonary valves (A). Deformation of one of the pulmonary valves (arrowhead) and dilatation of the pulmonary artery were observed (A). Ventricular septal defect (arrow) was formed at the membranous part of the ventricular septum (B). The right ventricular wall (asterisk) was thickened (C), and was approximately same as that of the left wall (B). LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

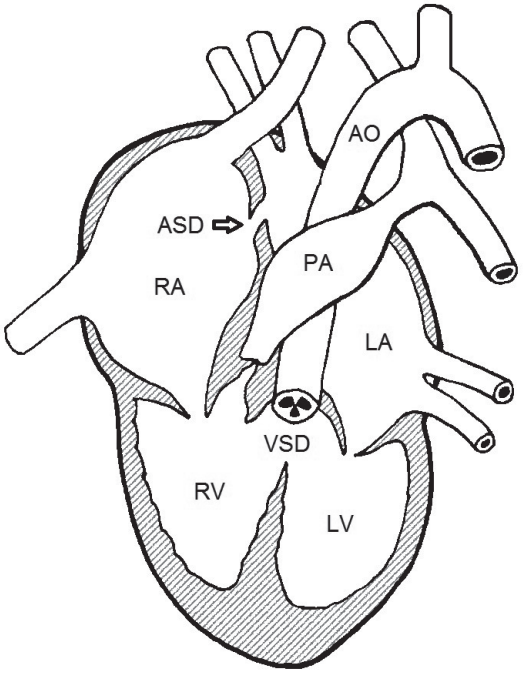

Fig. 2. A schematic diagram showing pentalogy of Fallot in a 19-month-old Holstein heifer. AO, aorta; ASD, atrial septal defect; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; VSD, ventricular septal defect.

PDA. The pulmonary stenosis, VSD, overriding aortic root, and ASD of the heifer in this study are likely to have been caused by developmental anomalies; while the right ventricular hypertrophy may have occurred as the result of pulmonary stenosis [33, 38]. Only 1 case of cattle with POF have previously been reported to live longer than 18 months, a 2-and-a-half year old Guernsey cattle with POF and without PDA [6]. Thus, the heifer in this study lived longest among the Holsteins reported to have had POF. McKenna *et al.* described a 2-year-old heifer with TOF and explained the factors that affect longevity, such as the size of the VSD and the degree of pulmonary stenosis [19]. The heifer in this study may have lived for 18 months secondary to mild pulmonary stenosis due to deformation of one of the pulmonary valves. It is likely that the pulmonary stenosis eventually progressed to the obstruction of the right ventricular outflow tract at the age of 18 months, which led to the heifer's death. The longevity of equines and humans with unrepaired TOF/POF depends mainly on the presence of PDA, or other alternative vessels that bypass the pulmonary artery [18, 23, 28, 34]. Extracardiac shunts, such as PDA, may also be one of the causes for the longevity of bovine specimens with TOF/POF, indicated from a Holstein heifer with TOF accompanied by PDA lived for 19 months [8]. It is unclear why the Guernsey cattle with POF (but lacked PDA) lived longer than the heifer in this study. Since the VSD size was smaller in the present case than in the Guernsey cattle [6], it may be due to the difference in the severity of pulmonary stenosis or the difference in breed.

The prevalence rate of pulmonary artery dilatation in bovine congenital heart disease is reported to be 2.5% [12], while those in bovine cases of TOF/POF and human TOF cases are not as likely to be low. Out of 24 cases of bovine TOF/POF, 5 cases thus far (including the present case) have been reported to accompany pulmonary artery dilatation [4–6, 8, 9, 12–14, 16, 17, 19–21, 24, 29, 30, 32, 36], which shows a prevalence rate of 20.8%. In humans, the expansion of the pulmonary artery is classified as either dilatation or aneurysm according to its diameter, and the prevalence of pulmonary artery dilatation or aneurysm in cases of TOF has been reported to be 20.5% [10]. It appears that pulmonary artery dilatation in cattle with TOF/POF is found at a comparable prevalence to that in humans. Pulmonary artery dilatation in humans is caused by increased pulmonary blood flow in large left-to-right shunts [3, 22] and the turbulence of blood flow caused by the abnormal opening of the pulmonary valve [11, 37, 39]. Human TOF with absent pulmonary valve syndrome, which is presumed to develop both of the above-mentioned hemodynamic effects, is reported to present with severe pulmonary artery dilatation [7, 10, 38]. Deformation of one of the pulmonary valves was observed in the heifer we are presenting, and it may be the cause of pulmonary artery dilatation.

In this study, an 18-month-old Holstein heifer with POF which had pulmonary artery dilatation and lacked PDA has been presented. This clinical case will update our current knowledge of the relationship between lifespan of bovine specimens with TOF/POF and the presence of PDA or pulmonary artery dilatation.

REFERENCES

1. Ali, N. 2015. Tetralogy of Fallot. *JAAPA* **28**: 65–66. [Medline] [CrossRef]
2. Angral, R., Sabesan, P., Natarajan, K. and Ninan, B. 2012. Inadvertent placement of left central venous catheter into left internal thoracic vein: a case report. *Ann. Card. Anaesth.* **15**: 165–166. [Medline] [CrossRef]
3. Boughner, D. R. and Roach, M. R. 1971. Etiology of pulmonary artery dilatation and hilar dance in atrial septal defect. *Circ. Res.* **28**: 415–425. [Medline] [CrossRef]
4. Breukink, H. J., Koneman, J. and Krediet, P. 1965. A Fallot's tetralogy in a Friesian calf. *Tijdschr. Diergeneeskd.* **90**: 1164–1176.
5. Cordy, D. R. and Ribelin, W. E. 1950. Six congenital cardiac anomalies in animals. *Cornell Vet.* **40**: 249–256. [Medline]
6. Dear, M. G. and Price, E. K. 1970. Complex congenital anomaly of a bovine heart. *Vet. Rec.* **86**: 219–222. [Medline] [CrossRef]
7. Emmanoulides, G. C., Thanopoulos, B., Siassi, B. and Fishbein, M. 1976. "Agenesis" of ductus arteriosus associated with the syndrome of tetralogy of Fallot and absent pulmonary valve. *Am. J. Cardiol.* **37**: 403–409. [Medline] [CrossRef]
8. Fisher, E. W. and Pirie, H. M. 1964. Tetralogy of fallot in a friesian heifer. *Br. Heart J.* **26**: 97–104. [Medline] [CrossRef]
9. Fisher, E. W. and Pirie, H. M. 1964. Malformations of the ventricular septal complex in cattle. *Br. Vet. J.* **120**: 253–272. [CrossRef]
10. Gallego, P., Rodríguez-Puras, M. J., Serrano Gotarredona, P., Valverde, I., Manso, B., González-Calle, A., Adsuar, A., Cubero, J. M., Díaz de la Llera, L., Ordoñez, A. and Hosseinpour, A. R. 2018. Prevalence and prognostic significance of pulmonary artery aneurysms in adults with congenital heart disease. *Int. J. Cardiol.* **270**: 120–125. [Medline] [CrossRef]
11. Guntheroth, W. G. 2002. Causes and effects of poststenotic dilation of the pulmonary trunk. *Am. J. Cardiol.* **89**: 774–776. [Medline] [CrossRef]
12. Hagio, M., Murakami, T. and Otsuka, H. 1987. Two-dimensional echocardiographic diagnosis of bovine congenital heart disease: echocardiographic and anatomic correlations. *Nippon Juigaku Zasshi* **49**: 883–894. [Medline] [CrossRef]
13. Hare, J. E., Baird, J. D., Duignan, P., Saunders, J., Floetenmeyer, R. and Basrur, P. K. 1994. XY gonadal dysgenesis and tetralogy of Fallot in an Angus calf. *Can. Vet. J.* **35**: 510–512. [Medline]
14. Jasper, D. E. 1948. Myocardial abscesses associated with a congenital cardiac defect in a heifer. *Cornell Vet.* **38**: 436–439.
15. Kemler, A. G. and Martin, J. E. 1972. Incidence of congenital cardiac defects in bovine fetuses. *Am. J. Vet. Res.* **33**: 249–251. [Medline]
16. Lacuata, A. Q., Yamada, H., Hirose, T. and Yanagiya, G. 1981. Tetralogy of Fallot in a heifer. *J. Am. Vet. Med. Assoc.* **178**: 830–836. [Medline]
17. Lane, V. M., Anderson, B. C. and Bulgin, M. S. 1983. Polycythemia and cyanosis associated with hypoplastic main pulmonary segment in the bovine heart. *J. Am. Vet. Med. Assoc.* **183**: 460–461. [Medline]
18. Liberthson, R. R., Miller, S. W., Drew, F., Palacios, I. and Singh, J. 1981. Congenital extracardiac shunts with tetralogy of Fallot. *Cardiovasc. Intervent. Radiol.* **4**: 131–135. [Medline] [CrossRef]
19. McKenna, S. L. B., Barkema, H. W., McClure, J. T. and Rogers, L. A. 2003. Tetralogy of Fallot in a 2-year-old Holstein heifer. *Can. Vet. J.* **44**: 312–313. [Medline]
20. Mohamed, T., Sato, H., Kurosawa, T., Oikawa, S., Nakade, T. and Koiwa, M. 2004. Tetralogy of Fallot in a calf: clinical, ultrasonographic, laboratory and postmortem findings. *J. Vet. Med. Sci.* **66**: 73–76. [Medline] [CrossRef]
21. Nakade, T., Uchida, Y. and Otomo, K. 1993. Three cases of bovine extreme tetralogy of Fallot. *J. Vet. Med. Sci.* **55**: 161–167. [Medline] [CrossRef]
22. Nguyen, E. T., Silva, C. I. S., Seely, J. M., Chong, S., Lee, K. S. and Müller, N. L. 2007. Pulmonary artery aneurysms and pseudoaneurysms in adults: findings at CT and radiography. *AJR Am. J. Roentgenol.* **188**: W126–34. [Medline] [CrossRef]
23. Nottestad, S. Y., Slife, D. M., Rubal, B. J. and Moody, J. M. Jr. 1993. Tetralogy of Fallot in a 71-year-old patient with new onset hypoxemia. *Cathet. Cardiovasc. Diagn.* **28**: 335–338. [Medline] [CrossRef]
24. Oshima, K. I. and Miura, S. 1972. A histopathological report on a case of histoplasmosis in a heifer with Fallot's tetralogy. *Nippon Juigaku Zasshi* **34**: 333–339. [Medline] [CrossRef]
25. Park, I. C., Lee, H. S., Kim, J. T., Lee, J. S., Lee, S. G. and Hyun, C. 2007. Pentalogy of Fallot in a Korean Sapsaree dog. *J. Vet. Med. Sci.* **69**: 73–76. [Medline] [CrossRef]
26. Pazzi, P., Lim, C. K. and Steyl, J. 2014. Tetralogy of Fallot and atrial septal defect in a white Bengal Tiger cub (Panthera tigris tigris). *Acta Vet. Scand.* **56**: 12. [Medline] [CrossRef]
27. Pielmeier, R., Engelke, E., Legler, M., Haist, V., Hopster-Iversen, C. and Distl, O. 2013. [Congenital cardiac anomalies (pentalogy of Fallot) in a two year old ram with brachygnathia inferior]. *Berl. Munch. Tierarztl. Wochenschr.* **126**: 256–263 (in German). [Medline]
28. Rahal, C., Collatos, C., Solano, M. and Bildfell, R. 1997. Pentology of Fallot, renal infarction and renal abscess in a mare. *J. Equine Vet. Sci.* **17**: 604–607. [CrossRef]
29. Reef, V. B. and Hattel, A. L. 1984. Echocardiographic detection of tetralogy of Fallot and myocardial abscesses in a calf. *Cornell Vet.* **74**: 81–95. [Medline]
30. Rehage, J., Veltmann, P., Stadler, P., Dieckmann, M., Poulsen-Nautrup, C. and Scholz, H. 1990. [Fallot's tetralogy in a calf—a case report]. *Dtsch. Tierarztl. Wochenschr.* **97**: 532–534 (in German). [Medline]
31. Scaglione, F. E., Tursi, M., Chiappino, L., Schröder, C., Triberti, O. and Bollo, E. 2012. Pentalogy of Fallot in a captive Siberian tiger (Panthera tigris altaica). *J. Zoo Wildl. Med.* **43**: 931–933. [Medline] [CrossRef]
32. Shirota, K., Saitoh, Y., Muto, M., Wakao, Y., Une, Y. and Nomura, Y. 1994. Crossed fat embolism in a cow with tetralogy of Fallot. *J. Vet. Med. Sci.* **56**: 969–971. [Medline] [CrossRef]
33. Starr, J. P. 2010. Tetralogy of fallot: yesterday and today. *World J. Surg.* **34**: 658–668. [Medline] [CrossRef]
34. Thomas, S. H., Bass, P., Pambakian, H. and Marigold, J. H. 1987. Cyanotic tetralogy of Fallot in a 77 year old man. *Postgrad. Med. J.* **63**: 361–362. [Medline] [CrossRef]
35. van der Linde, D., Konings, E. E. M., Slager, M. A., Witsenburg, M., Helbing, W. A., Takkenberg, J. J. M. and Roos-Hesselink, J. W. 2011. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J. Am. Coll. Cardiol.* **58**: 2241–2247. [Medline] [CrossRef]
36. van Nie, C. J. 1983. The conduction system in cattle hearts with ventricular septal defects. *Anat. Histol. Embryol.* **12**: 289–294. [Medline] [CrossRef]
37. Veldtman, G. R., Dearani, J. A. and Warnes, C. A. 2003. Low pressure giant pulmonary artery aneurysms in the adult: natural history and management strategies. *Heart* **89**: 1067–1070. [Medline] [CrossRef]
38. Wise-Faberowski, L., Asija, R. and McElhinney, D. B. 2019. Tetralogy of Fallot: Everything you wanted to know but were afraid to ask. *Paediatr. Anaesth.* **29**: 475–482. [Medline] [CrossRef]
39. Yamanaka, K., Shiiya, N., Yamashita, K., Washiyama, N., Takahashi, D., Sakagami, N. and Natsume, K. 2016. Pulmonary artery aneurysm associated with a unicuspid pulmonary valve. *J. Card. Surg.* **31**: 745–746. [Medline] [CrossRef]