Clostridial myonecrosis, haemolytic anaemia, hepatopathy, osteitis and transient hypertrophic cardiomyopathy after intramuscular injection in a Thoroughbred gelding

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Abstract

A 9-year-old Thoroughbred gelding was presented for swelling over the left neck and inappetence. There was recent history of intramuscular administration of flunixin meglumine into the left neck. On examination, there was evidence of focal myositis, anaemia, haemolysis and pigmenturia. Culture of aspirated fluid from the left side of the neck produced a heavy growth of a *Clostridium* species. Complications of infection included haemolytic anaemia, hepatopathy, osteitis and transient hypertrophic cardiomyopathy. Treatment included intravenous fluid therapy, antibiotics, anti-inflammatory drugs, blood transfusion and surgical debridement. There was complete resolution of clinical, haematological, biochemical and echocardiographic abnormalities, and the horse returned to ridden work. This report highlights the complications that can arise from clostridial myonecrosis, including the effect on the myocardium.

Keywords: cardiomyopathy; clostridial myonecrosis; haemolytic anaemia; horses

Abbreviations

cTnI - cardiac troponin I

FS - fractional shortening

IMHA - immune-mediated haemolytic anaemia

NSAID - non-steroidal anti-inflammatory drug

PCV - packed cell volume

USG - urine specific gravity

Clostridial myonecrosis is a well-described and potentially fatal disease of horses.[1-5] There are several species of *Clostridia* associated with myonecrosis including, but not limited to, *Cl. perfringens, Cl. septicum, Cl. chauvoei* and *Cl. novyi*.[1] The majority of cases have been associated with recent intramuscular injection of commonly used therapeutic agents,[1] although infection can follow trauma.[2]Complications of infection also include haemolytic anaemia.[4] This report describes the presentation of a 9-year-old Thoroughbred gelding for treatment of a clostridial myonecrosis associated with an intramuscular injection of flunixin meglumine. The horse was moderately anaemic because of haemolysis and required a blood transfusion to facilitate surgical debridement of the wound. Further complications of the clostridial infection in this case included hepatopathy, osteopathy of the cervical vertebrae and a transient hypertrophic cardiomyopathy. Direct cardiac complications have not been reported as a sequela to clostridial infection.

Case Report

A 9-year-old Thoroughbred gelding was initially treated by a veterinarian for a suspected large colon impaction 15 days prior to referral. The horse was treated symptomatically by the referring veterinarian with nasogastric administration of mineral oil and electrolytes, and flunixin meglumine (1500 mg IV). The horse continued to show mild persistent abdominal pain and the owners administered flunixin meglumine intramuscularly at approximately 12-h intervals on three occasions (1500 mg, 1000 mg and 1000 mg). At 24 h after the first intramuscular injection, the horse became inappetent, was unable to raise his neck and had a painful focal swelling in the area where the initial intramuscular injection had been administered, prompting re-examination by the attending veterinarian. The signs of abdominal pain had resolved and physical examination confirmed neck pain and swelling and ulceration of the oral mucosa. Additional therapy at that time included phenylbutazone, corticosteroids (dexamethasone 100 mg IV on one occasion) and antibiotics. Procaine penicillin (10,000 U/kg IM every 12 h) was given for 48 h and then replaced with trimethoprim–sulfadimidine (30 mg/kg PO every 12 h). Phenylbutazone was continued at a dose rate of 2.2 mg/kg PO every 12 h. Over the following 10 days the left cervical swelling slowly became more pronounced and painful with crepitus. The gelding was referred when red fluid was seen dripping from the prepuce 15 days after the initial episode of abdominal pain.

On presentation at Murdoch University Veterinary Hospital, the horse weighed 450 kg, was in poor body condition (body condition score 3/9), quiet and febrile (38.8°C). Mucous membranes were pale, tacky and icteric, with a capillary refill time of 3 s. Superficial oral ulceration was noted at this time. Cardiac auscultation revealed tachycardia (80 beats/min),

with a normal rhythm and no audible murmur. Respiratory rate and thoracic auscultation during re-breathing examination were within acceptable limits. The left side of the neck was markedly swollen, warm and painful to the touch and crepitus was noted from the base of the left ear to the distal third of the neck. Forelimb digital pulses were moderately increased and the horse constantly shifted weight between forelimbs when standing on firm ground. Auscultation of the abdomen revealed normal gastrointestinal sounds in all quadrants. Dark red urine was voided during the examination and a free catch sample was submitted for analysis.

Blood was collected into an EDTA anticoagulant and a serum tube for analysis. Initial laboratory abnormalities included gross evidence of intravascular haemolysis, icterus and autoagglutination. A complete blood count revealed moderate anaemia (haematocrit 0.19L/L, reference range 0.31–0.50L/L), leucocytosis (24.2×10^9/L, reference range 4.3–14.8×10^9L) with a mature neutrophilia (22.8×10^9/L, reference range 2.2–8.1×10^9/L), lymphopenia (0.7×10^9/L, reference range 1.7–5.8×10^9/L), thrombocytopenia (45×10^9/L, reference range 100–251×10^9/L) and hyperfibrinogenaemia (5 g/L, reference range 0–4 g/L). Biochemical abnormalities included elevated concentrations of aspartate transferase (2306 IU/L, reference range 226–366 IU/L), creatine kinase (8081 IU/L, reference range 100–500 IU/L), gamma glutamyltransferase (89 IU/L, reference range 19–50 IU/L), glutamate dehydrogenase (131 U/L, reference range 0–10 U/L), total bilirubin (203 IU/L, reference range 0–85 IU/L) and serum bile acids (28 μmol/L reference range 0–18 μmol/L). Elevated total protein concentration (79 g/L, reference range 52–78 g/L) was primarily attributed to an increase in globulins (50.1 g/L, reference range 26–40 g/L). Venous blood gas was within normal limits. Autoagglutination precluded performing a direct Coomb's test.

Urinalysis revealed a normal specific gravity (1.035) and no evidence of casts on cytology. There was a strong positive reaction for haemoprotein on reagent strip (Bayer N-Multistix® SG Reagent Strips). Haematuria was not evident and it was assumed that both haemoglobin and myoglobin contributed to the positive test result.

Ultrasound of the thoracic and abdominal cavities was within normal limits. Ultrasound of the neck region revealed two large areas of fluid with mixed echogenicity that extended into the underlying musculature. Fluid was aspirated aseptically from the fluid pockets and submitted for Gram-stain, cytology, culture (aerobic and anaerobic) and antimicrobial sensitivity testing. The presence of intra- and extracellular Gram-positive rods indicated likely clostridial infection, which was confirmed by culture 48 h later. The laboratory reported the isolate as probable *Cl. perfringens*.

Tetanus toxoid was administered intramuscularly. An over-the-wire polyurethane catheter (Mila^{TM}) was placed into the right jugular vein. Polyionic, isotonic fluids (Hartmann's solution) further supplemented with potassium chloride (20 mEq/L) and calcium borogluconate (25 mL of 40% solution added per litre) were administered initially at 5 mL/kg/h, then reduced to 2.5 mL/kg/h after 24 h. The horse had free access to both plain water and water supplemented with electrolytes. Appetite slowly improved over the initial 24 h of hospitalisation. The horse was treated with sodium ceftiofur (2.2 mg/kg IV every 12h) and metronidazole (20 mg/kg PO every 8h).

By day 2 the thrombocytopenia had resolved, but the packed cell volume (PCV) had decreased to 15%, most likely because of intravenous fluid resuscitation and continued haemolysis. Prior to surgical debridement of the left side of the neck, 6 L of citrated whole blood was administered to the patient (the donor was Donor Aa-negative, Qa-negative and negative for anti-Aa and anti-Qa antibodies). Standing surgery resulted in the draining of several litres of fetid fluid from two sites on the left neck. The surgical site was packed with saline-soaked sponges and the wound was lavaged and re-dressed twice daily.

Lateral radiographs of both front feet were taken on day 2 because the horse was shifting weight, had increased digital pulses and pain on hoof testers. There was no evidence of rotation of the distal phalanx, with adequate depth of sole, but there was evidence of chronic, severe modelling of the distal phalanx. The clinical and radiographic signs were supportive of an acute exacerbation of chronic laminitis.

Non-steroidal anti-inflammatory drug (NSAID) toxicity was considered, given the mucosal ulceration and recent administration of high doses of NSAIDs in conjunction with apparent hypovolemia. It was decided to continue appropriate but less frequent doses of flunixin meglumine (1.1 mg/kg IV every 24 h) because of the ongoing myonecrosis and toxaemia. Misoprostal (2 µg/kg PO every 8 h), sucralfate (40 mg/kg PO every 8h) and omeprazole (1 mg/kg PO every 24 h) were added to the treatment plan. Intravenous fluids were continued at a maintenance rate (2 mL/kg/h) throughout the remainder of the first week of hospitalisation. Urinalysis, including fractional excretion rates of several electrolytes, was normal 24 h after discontinuation of IV fluids.

Persistent tachycardia (>80 beats/min) was not adequately explained by the magnitude of anaemia or musculoskeletal pain. Electrocardiographic examination on day 5 revealed sinus tachycardia, but no other abnormalities. The tachycardia did not resolve following intravenous supplementation with magnesium sulfate. The cardiac troponin I (cTnI) concentration was moderately elevated at 0.17 μg/L (reference range <0.04 μg/L). Echocardiography revealed marked thickening of the interventricular septum and left ventricular free wall, with decreased dimensions of the left ventricular cavity (Table 1; Figure 1), resulting in an abnormal shape. Fractional shortening (FS) was increased. The combination of increased cTnI and the abnormal echocardiographic findings, in conjunction with apparent normovolaemia, was consistent with a myocardial insult (transient hypertrophic cardiomyopathy).

The PCV continued to decrease despite treatment and on day 11 was 8%. There was concern the continued anaemia may be related to beta-lactam antibiotic-induced red cell haemolysis, resulting in the replacement of sodium ceftiofur with doxycyline (10 mg/kg PO every 12 h). The horse remained on metronidazole. Azathioprine was commenced (2 mg/kg PO every 24h) and decreased to 1 mg/kg PO every 24 h after 10 days, and discontinued after 25 days of treatment. The haematocrit rose concurrently with these drug changes and continued management of the underlying clostridial infection.

The horse was discharged from hospital on day 19 to continue treatment with doxycycline and metronidazole, which were discontinued on days 65 and 50, respectively. At the time of discharge (day 19), the heart rate had improved, but remained mildly elevated (44–48 beats/min). The haematocrit was 0.19 L/L and serum cTnI was normal (<0.04 μg/L).

Echocardiographic measurements had also improved (Table 1). Total bilirubin (91 μmol/L) and globulins (51.9 g/L) were elevated at initial discharge, but had normalised at re-examination on day 37. Echocardiographic examination on day 37 was normal (Table 1, Figure 2).

The horse presented a third time on day 57 because of persistent discharge from one of the cervical surgery sites, localised pain and suspected focal neural involvement, as evidenced by spontaneous hemifacial spasm and localised muscular twitching in the upper neck. Ultrasound examination of the upper cervical region cranial and dorsal to the discharging sinus revealed a tract that extended to the level of the left aspect of the atlas. Lateral and dorsal–ventral radiographs were taken of this region, but showed no osseous abnormalities. A general anaesthetic and surgical debridement were performed. The tract was explored from the point of drainage on the left neck, cranially and dorsally to the wing of the atlas, which was roughened and irregular in appearance at its lateral margin. The tendon of the longissimus capitus was conserved. The lining of the tract was resected and the involved bone removed and curetted. Culture of the bone and tissue removed during surgery failed to yield any bacteria. The horse was placed perioperatively on sodium ceftiofur (2.2 mg/kg IV every 12 h). The hemifacial spasm and muscular twitching completely resolved post-surgery and the horse recovered without further incident. The horse continued to gain weight and 8 months after the initial insult had returned to light ridden work.

Discussion

This case demonstrates the serious complications that can occur following intramuscular injections. This horse developed clostridial myositis subsequent to intramuscular flunixin meglumine, as well as haemolytic anaemia, hepatopathy, osteitis and transient hypertrophic cardiomyopathy. Clostridial myonecrosis in horses has been widely reported in the scientific literature.[1-5] The disease is induced through a range of events and resultant clinical manifestations are variable. The precipitating event in this case was probably an intramuscular injection of flunixin meglumine. Other drugs that have been associated with clostridial infection include ivermectin, antihistamines, phenylbutazone, dipyrone, vitamin B complex, aminopropazine and synthetic prostaglandin.[1, 5] Infection occurs less commonly as a result of traumatic wounds.[2, 7] The reported survival rate from clostridial myositis is very low,[6] but a recent study reported improved survival when there is rapid diagnosis and intervention.[1]

The case reported here demonstrates some of the important complications of clostridial myonecrosis. The presence of immune-mediated haemolytic anaemia (IMHA) is an infrequent but well-described complication of clostridial infection in horses.[3, 4, 8] There was evidence of both intra- and extravascular hemolysis in this case. The intravascular haemolysis was reflected in the discoloured plasma and red urine in the early period of hospitalisation. Sustained extravascular haemolysis was likely on the basis of declining haematocrit, bilirubinaemia and bilirubinuria in the absence of pink discoloration of plasma and urine later in the period of hospitalisation. IMHA was the probable basis of the haemolysis and was supported by the presence of autoagglutination. IMHA has been reported in association with a range of systemic bacterial and viral diseases, including clostridial myonecrosis.[3, 4, 9] The basis of IMHA in response to clostridial infection is unknown, with one theory suggesting toxin-induced damage to erythrocyte membranes causes exposure or

alteration of antigens, inducing an immune response.[3] The diagnosis of IMHA may be confirmed by a positive direct antiglobulin (DAT)/Coomb's test, but the sensitivity of this test has been reported to be low.[10] The horse in this case was not tested at admission because of the spontaneous autoagglutination. A direct immunofluorescence assay with flow cytometry for erythrocyte antibodies was unavailable.

IMHA will typically resolve following removal or treatment of the primary inciting cause. Blood transfusion is not always necessary, but was justified in this case because of anticipated losses of blood during the surgical debridement that was an important component of successful case management.[1] Corticosteroids have been used in refractory cases of IMHA,[11, 12] but their use in this case was considered inappropriate as they are detrimental to tissue healing[13, 14] and are associated with an increased risk of laminitis.[15] Azathioprine is used to treat both autoimmune and immune-mediated conditions in human and veterinary medicine. Drug bioavailability is lower and elimination faster than in humans,[16] resulting in concern over its efficacy in horses. However, azathioprine has been used to successfully treat a range of immune-mediated disorders in horses.[17-20] Haematologically, it is difficult to ascribe the immediate improvement in PCV to azathioprine, as clinical response in humans is not immediate.[21] The horse was monitored for bone marrow suppression and hepatotoxicity, two complications of azathioprine therapy.[17] Ceftiofur sodium was concurrently discontinued in the unlikely event it was responsible for ongoing haemolytic anaemia and therefore its discontinuation may have contributed to the resolution of the anaemia. Doxycycline was thought an appropriate replacement because it was reported to have good efficacy against *Cl. perfringens* in a murine model.[22]

Elevations in total bilirubin, gamma glutamyltransferase and glutamate dehydrogenase at admission support the diagnosis of hepatobiliary injury and dysfunction. Elevations in the concentration of serum bile acids confirm liver dysfunction, which may be attributed to hepatocyte damage, prolonged fasting or blockage of bile flow.[23] In this case, the hepatopathy was not considered of sufficient severity to be the primary cause of haemolysis. Normalisation in hepatobiliary enzymes occurred with improvement in the myositis and anaemia, indicating hepatopathy was possibly from tissue hypoxia, myocardial damage and the effects of clostridial toxins. Thrombocytopenia at admission may have been caused by chronic, compensated disseminated intravascular coagulation initiated by the neck abscess, immune-mediated thrombocytopenia, local consumption of platelets, EDTA-associated pseudothrombocytopenia or other unidentified causes.

To our knowledge, this is the first report to document primary cardiac changes with clostridial myonecrosis, though a single case of clostridial myonecrosis resulting in septic pericarditis in a horse is reported.[24] Diagnosis of hypertrophic cardiomyopathy was made following several days of unexplained persistent tachycardia, elevation of serum cTnI concentration and echocardiographic findings. Troponin is a 3-unit complex, comprising TnT, TnC and TnI, and is required for calcium-mediated regulation of cardiac and skeletal muscle contraction.[25] Elevation in the cTnI concentration is a consistent finding with myocardial disease in humans [26, 27] and animals, including horses.[28] Elevations can also occur with renal disease, pulmonary embolism and toxaemia.[27, 29] It is difficult to confirm a diagnosis of myocarditis without more advanced diagnostic evaluation. Definitive diagnosis of myocarditis in humans can be made using endomyocardial biopsy, nuclear imaging and magnetic resonance imaging, [26] but these diagnostic modalities are generally unavailable in large animal medicine. In many cases the inciting cause of the myocardial insult is not

determined. Cardiomyopathy in horses has been attributed to viral or bacterial infection or plant and drug toxicoses.[30] Experimentally, exogenous endotoxin will cause an acute rise in the cTnI concentration in normal horses, indicating myocardial injury.[31] It is difficult to determine if clostridial bacteria were the direct cause of the myocardial injury or it resulted from bacterial exotoxins, as has been described with other clostridial infections such as *Cl. sordelli*.[32]Immune-mediated myocardial injury is uncommon, though possible in this case.

Echocardiography is a useful tool for identifying myocardial injury. Findings associated with myocarditis in human beings are varied and non-specific.[26, 33] Common changes include segmental wall motion abnormalities and reversible left ventricular hypertrophy.[26] The pertinent echocardiographic changes in the present case include reversible concentric left ventricular hypertrophy with decreased size of the left ventricular cavity. It is recognised that hypohydrated horses can have changes in the size of both the left ventricle and atrium that may be interpreted as hypertrophy, termed ‘pseudohypertrophy’, as the cardiac abnormalities resolve with correction of dehydration.[34]The first cardiac ultrasound examination of the present horse was performed on day 5 post-admission when hydration status was considered normal as assessed by normal lactate and urine output. Therefore, the cardiac abnormalities observed were unlikely to be ‘pseudohypertrophy’ resulting from dehydration. Intravenous fluid therapy was being administered at a maintenance rate at this time because of the mild pigmenturia and the excessive administration of NSAIDs prior to admission. Increased FS is not commonly reported in horses with myocardial injury. It is more common to detect reduced contractility and therefore a decreasing FS. Given the concentric left ventricular hypertrophy with a reduction in the dimensions of the left ventricular cavity, it is reasonable to expect the observed increase in FS in the present case.

Treatment of myocardial injury and myocarditis in humans is largely supportive, though immunomodulating agents have been used when immune-mediated causes are suspected or confirmed.[26] In this case, the horse was managed through continued supportive therapy and treatment of the primary clostridial infection. Resolution was based on normalisation of repeated echocardiographic examination and cTnI concentration. Given that the origin of the myocardial damage is unknown, it would be speculative to suggest that azathioprine was of significant benefit in this case. Azathioprine has been used as a treatment of myocardial inflammation in humans and thought to be of benefit if the origin is systemic autoimmune disease.[26]

This case highlights the severe complications that may occur with the intramuscular injection of commonly used therapeutic agents such as flunixin meglumine. It is proposed that tissue damage by such therapeutic agents may create a favourable environment for activation of resident clostridial spores.[35] It is therefore advisable to administer all medications carefully via intravenous routes, if registered for this route of delivery, or with appropriate care to minimise trauma if intramuscular injection is required. Myocardial injury should be considered in the event of unexplained persistent tachycardia in horses with underlying sepsis. Echocardiography and serial measurement of serum cTnI concentration are useful in increasing the accuracy of diagnosis of myocardial injury and monitoring response to treatment.

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Figure 1. Two-dimensional and M-mode echocardiography of a horse that was hospitalised following clostridial myositis. The echocardiogram on day 5 demonstrates thickening of the interventricular septum and left ventricular free wall with a reduction in the dimensions of the left ventricular cavity. (Obtained using a Phillips CX-50 with a S5-1 transducer at the right parasternal cardiac window. Maximum field depth 27 cm.)

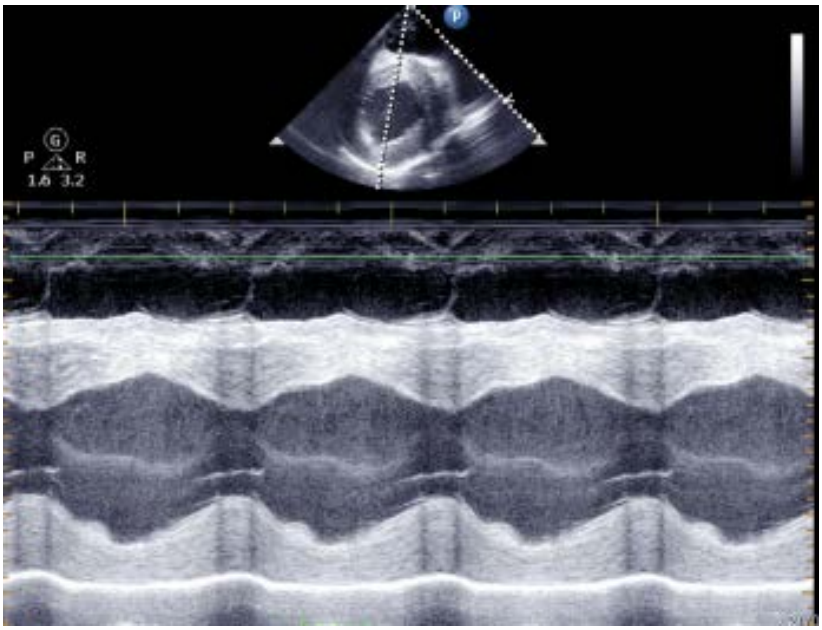

Figure 2. Two-dimensional and M-mode echocardiography of the same horse on day 37 following treatment for clostridial myositis, demonstrating normal cardiac dimensions. (Obtained using a Phillips CX-50 with a S5-1 transducer at the right parasternal cardiac window. Maximum field depth 27 cm.)

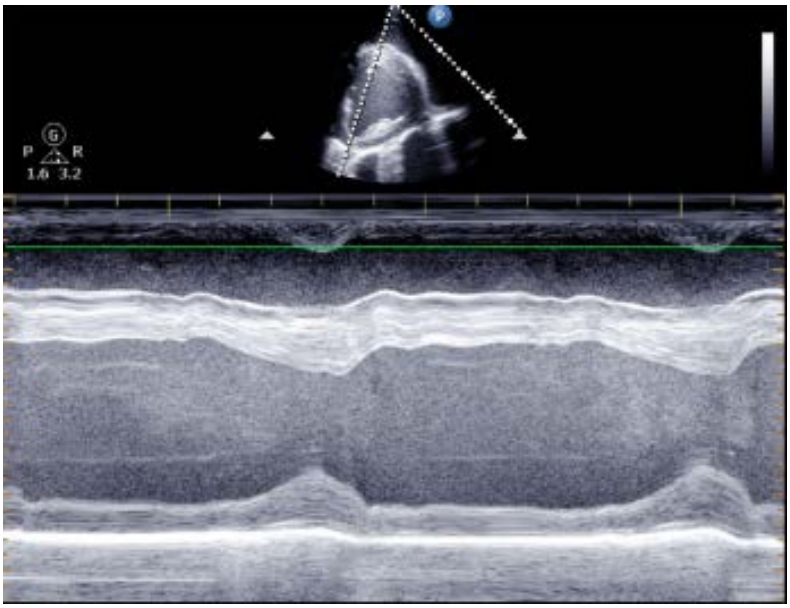

Table 1. Serial echocardiographic measurements of the horse documenting the left ventricular hypertrophy and resolution of the cardiac abnormalities following treatment

Variable	Published mean echocardiography values[6]	Published normal values for standard deviation[6]	Day 5[a]	Day 23[a]	Day 37[a]
IVSd (cm)	2.85	0.278	4.2	3.2	2.9
LVIDd (cm)	11.92	0.760	10.9	11.8	11.3
LVPWd (cm)	2.32	0.382	2.6	2.6	2.5
IVSs (cm)	4.21	0.463	5.9	5.2	4.5
LVIDs (cm)	7.45	0.615	5.9	6.3	7.0
LVPWs (cm)	3.85	0.414	4.8	4.4	3.9
FS (%)	37.42	3.860	50.3	46.4	37.6

[a] Obtained using a Phillips CX-50 with a S5-1 transducer at the right parasternal cardiac window.
IVSd, interventricular septal thickness systole; LVIDd, left ventricular internal diameter diastole; LVPWd, left ventricular posterior wall diastole; IVSs, interventricular septum in systole; LVIDs left ventricular internal diameter systole; LVPWs, left ventricular posterior wall systole; FS, fractional shortening.