

Cardiac Troponin I as Compared to Troponin T for the Detection of Myocardial Damage in Horses

N. Van Der Vekens, A. Decloedt, S. Ven, D. De Clercq, and G. van Loon

Background: Different cardiac troponin I (cTnI) assays give different results. Only 1 manufacturer has marketed troponin T (cTnT) assays. Therefore, cTnT often is preferred for detection of myocardial infarction in human patients. Studies of cTnT in horses are limited.

Objectives: To compare a cTnI and a high-sensitive cTnT assay (hs-cTnT) in horses.

Animals: Cardiac troponin I and cTnT were determined in 35 healthy horses (group 1), 23 horses suspected to have primary myocardial damage (group 2a), and 41 horses with secondary myocardial damage caused by structural heart disease (group 2b).

Methods: All cTnI samples were analyzed at laboratory A (limit of detection [LOD]: 0.03 ng/mL), whereas cTnT samples were analyzed at 2 laboratories with the same hs-cTnT assay (laboratory B, LOD: 10.0 pg/mL; laboratory C, LOD: 4.0 pg/mL).

Results: The median cTnI concentration in group 2a (0.90 ng/mL; range, 0.03–58.27 ng/mL) was significantly higher ($P < .001$) than in group 1 (0.03 ng/mL; range, 0.03–0.09 ng/mL) or group 2b (0.05 ng/mL; range, 0.03–30.92 ng/mL), and the optimal cut-off for detection of primary myocardial damage was 0.095 ng/mL (sensitivity: 90.5%, specificity: 100%). Using an LOD of 10.0 pg/mL for all cTnT samples, a cut-off value of 10.5 pg/mL was found, but sensitivity was low (42.9%). When only samples analyzed at laboratory C ($n = 58$) were included, a cut-off of 6.6 pg/mL was found (sensitivity: 81%, specificity: 100%).

Conclusions and Clinical Importance: Despite large quantitative differences, cTnI and cTnT are both useful for detection of myocardial damage in horses.

Key words: Atypical myopathy; Cardiac biomarkers; Valvular regurgitation.

Cardiac troponin I (cTnI) and troponin T (cTnT) have proven to be excellent cardiac biomarkers for diagnosis of myocardial injury in human medical practice.¹ They have replaced the less sensitive lactate dehydrogenase and creatine kinase-myocardial band enzymes since the 1990s and are routinely used in human patients for detection of acute myocardial infarction.^{2,3} Although cTnI and cTnT have comparable diagnostic efficacy, cTnT often is preferred in human medicine.³ The existence of a wide variety of cTnI assays from different manufacturers complicates interpretation and comparison of cTnI data.⁴ In contrast, only Roche Diagnostics^a has marketed cTnT assays.^{1,5}

The troponin structure is very conserved among species. Therefore, assays intended for humans can be used in horses and other animals.^{6,7} Over the last 15 years, measurement of cTnI has been introduced in equine veterinary medicine and several cTnI reference

Abbreviations:

AUC	area under the curve
cTnI	cardiac troponin I
cTnT	cardiac troponin T
hs-cTnT	high-sensitive cardiac troponin T
LDH	lactate dehydrogenase
LOD	limit of detection
ROC	receiving operator characteristic

ranges have been determined by different assays.^{8–13} Studies of cTnT measurement in horses are limited.^{14–16} Normal concentrations for cTnT were obtained in foals with a third generation Elecsys 2010^a immunoassay¹⁶ and in 20 healthy horses, by a qualitative cTnT assay (Trop T Sensitive Rapid Assay^a) and a quantitative cTnT enzyme-linked immunosorbent assay^b.¹⁵ In this last study, cTnT was increased in horses with cardiac diseases such as valvular insufficiency, endocarditis, and atypical myopathy. However, many horses with cardiac disease still had cTnT concentrations under the LOD of the assay (<40 pg/mL). Since 2010, Roche Diagnostics has marketed a new hs-cTnT assay.¹⁷ Because of its higher sensitivity and increased precision, this hs-cTnT assay may be a good alternative for cTnI measurement in horses. Laboratories often only provide cTnI or cTnT analysis. Therefore, additional cTnT studies in horses are needed to determine the applicability of cTnT measurement for the diagnosis of myocardial damage in horses. The aim of this study was to establish reference ranges for hs-cTnT in normal horses and to compare a cTnI with a hs-cTnT assay in healthy horses and horses with confirmed cardiac disease.

From the Department of Large Animal Internal Medicine, Faculty of Veterinary Medicine, Ghent University, Ghent, Belgium (Van Der Vekens, Decloedt, Ven, De Clercq, van Loon).

The work was performed at the Faculty of Veterinary Medicine (Merelbeke, Belgium), Department of Large Animal Internal Medicine.

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Corresponding author: N. Van Der Vekens, Salisburylaan 133, 9820 Merelbeke, Belgium; e-mail: nicky.vandervekens@ugent.be.

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Materials and Methods

Study Population

This study was approved by the ethics committee of the Faculty of Veterinary Medicine and Bioscience Engineering (EC2012_57). All horses were privately owned and examined with the owners' informed consent. To be included as control horses (group 1, $n = 35$), horses had to be healthy and in training, and had to be free of cardiac disease based on cardiac examination including echocardiography, electrocardiography (ECG) at rest and during exercise (Televet 100°).¹⁸ Horses of group 2 ($n = 64$) were presented at the Faculty of Veterinary Medicine with cardiac disease.

Data Collection and Analysis

Blood was collected before exercise by jugular venipuncture using a vacutainer collection tube. Samples were left at room temperature for 30 minutes to allow clotting. Next, they were centrifuged for 10 minutes at $2,576 \times g$. The serum was transferred into 3 cryovial tubes^d and stored at -20°C until sample analysis. Samples were transported on ice to 3 different laboratories (A, B and C; Fig 1). In laboratory A, all samples were analyzed with the Beckman Access Accu cTnI assay.^c The LOD of this assay was 0.03 ng/mL. Samples from all 99 horses also were analyzed with the hs-cTnT Troponin T hs assay: 47 samples (21 healthy horses and 26 horses with cardiac disease) were analyzed in laboratory B with the Cobas E602 analyzer and 58 samples (20 healthy horses and 38 horses with cardiac disease) were analyzed in laboratory C with the Cobas E601 analyzer (Fig 1). Six samples from healthy horses were analyzed both in laboratories B and C. In laboratory B, a LOD of 10.0 pg/mL was used. Although the same assay was used, the LOD of laboratory C was 4.0 pg/mL.

Statistical Analysis

Statistical analysis was performed by commercially available computer software (SPSS^f and MedCalc^g). Because data were not normally distributed, all results were reported as median and range (minimum, maximum), unless stated otherwise. Samples with a cTnI or cTnT concentration under the LOD (eg, <10.0 pg/mL) were assigned the concentration of the LOD (eg, 10.0 pg/mL). This allowed inclusion of all samples for further statistical

analysis. Because these samples probably had a lower troponin concentration than assigned, differences among groups were likely not overestimated, but rather underestimated. Initially, we chose to report all cTnT samples, including samples of laboratory C, with an LOD of 10.0 pg/mL. Secondly, only cTnT samples of laboratory C were considered, allowing an LOD of 4.0 pg/mL. The storage time difference between laboratories was compared by the nonparametric Friedman test. A nonparametric Mann-Whitney *U*-test was used to compare the horses' age, weight, and height. The troponin concentrations of group 1, 2a, and 2b were compared by the Kruskal-Wallis and the posthoc Dunn's test. The cTnI and hs-cTnT assays were compared after log transformation with the Spearman correlation test. A receiving operator characteristic (ROC) curve was established to determine the optimal cut-off value for detection of myocardial damage for both assays.

Results

Clinical, Echocardiographic, and Electrocardiographic Examination

Group 1 (age: 8 ± 4 years; weight: 540 ± 61 kg; height: 165 ± 6 cm) consisted of 13 geldings, 20 mares, and 2 stallions; 24 Warmbloods, 10 Trotters, and 1 pony. Group 2 (age: 10 ± 7 years; weight: 507 ± 97 kg; height: 163 ± 10 cm) consisted of 33 geldings, 28 mares, and 3 stallions; 39 Warmbloods, 4 mixed breeds, 5 ponies, 4 Friesians, 3 Trotters, 2 draft horses, 2 Quarter horses, 2 Spanish horses, 2 Arabian horses, and 1 Halflinger horse. No significant differences in age, weight, or height were found between horses of groups 1 and 2. Based on clinical and cardiac examination, horses of group 2 were divided into 2 subgroups: horses with primary myocardial disease (inflammatory, toxic, or ischemic myocardial damage) and horses with secondary myocardial disease caused by structural heart disease (valvular heart disease, ventricular septal defects, or aortopulmonary fistula).

Of the 64 horses with cardiac disease, 23 were diagnosed with primary myocardial disease and included in group 2a. Twenty-one horses were suspected to have atypical myopathy based on the seasonality of the disease, the presence of Maple trees (*Acer pseudoplatanus*) around the pastures, extremely increased muscle enzymes activity (creatin kinase: median, 69,750 mU/mL, range, 1,200–309,000), and necropsy.^{19,20} The remaining 2 horses in group 2a were suspected to have primary myocardial disease based on the presence of a large number of ventricular premature depolarizations ($>14/\text{minute}$) on ECG and lack of echocardiographic evidence of valvular, pericardial, or vascular disease. One of these horses also had ataxia, fever, and decreased systolic function of the left ventricle. Forty-one horses of group 2 were diagnosed with structural heart disease and therefore included in group 2b. The severity of valvular regurgitation in these horses was graded subjectively on a scale from 1 to 9.²¹ Grade 1–3 was classified as trivial regurgitation, grade 4–5 as mild, grade 6–7 as moderate, and grade 8–9 as severe valvular regurgitation, only horses with moderate or severe valvular regurgitation were selected. Fourteen horses had moderate regurgitation and 27 horses severe regurgitation of ≥ 1 valves. Within this group, 3 horses

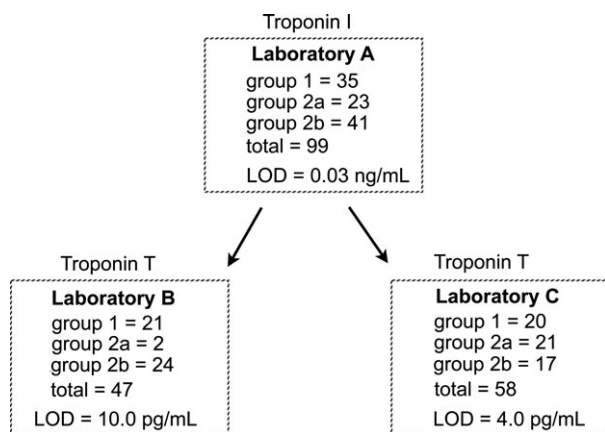


Fig 1. Schematic representation of sample analysis in the different laboratories (LOD, limit of detection; group 1, healthy horses; group 2a, horses with primary myocardial damage; group 2b, horses with secondary myocardial damage).

also had an aortapulmonary fistula and 4 horses had a ventricular septal defect.

Troponin Analysis

All samples were stored at -20°C according to the manufacturer's instructions and thawed only once. A maximum storage time of 6 months at -20°C was recommended by the manufacturer for the Access Accu cTnI assay. The median time until analysis for this assay was 2 days (range, 0–165 days). The maximum recommended storage time for the hs-cTnT assay was 12 months at -20°C . The median time until analysis was 5 days (range, 0–38 days) in laboratory B and 3 days (range, 0–183 days) for the hs-cTnT assay in laboratory C. The storage time of samples for laboratory A ($P = .002$) and C ($P = .005$) was significantly shorter than that of samples for laboratory C. No significant difference in storage time was found between laboratory A and laboratory C.

Most healthy horses had cTnI and cTnT concentrations under the LOD (cTnI: 0.03 ng/mL; cTnT: 10.0 pg/mL). The median (range) cTnI concentrations in horses of group 1, 2a, and 2b were 0.03 (0.03–0.09) ng/mL, 0.90 (0.03–58.27) ng/mL, and 0.05 (0.03–30.92) ng/mL, respectively. Horses of group 2a had significantly higher cTnI concentrations compared to horses of group 1 ($P < .001$) and group 2b ($P < .001$). Horses with secondary myocardial disease caused by structural heart disease (group 2b) also had significantly higher ($P = .003$) cTnI concentrations than healthy horses (group 1; Fig 2). Based on the ROC curve (Fig 3), an optimal cut-off value for detection of primary myocardial damage was determined for cTnI (0.095 ng/mL; area under the curve [AUC]: 0.94; 95% CI: 0.86–1.00; $P < .001$; sensitivity: 90.5%; specificity: 100%). No significant ($P = .051$) cut-off value (0.045 ng/mL) could be determined for detection of secondary myocardial damage.

The median (range) cTnT concentration also was significantly ($P = .001$) higher in group 2a (10.0, 10.0–2,010.0 pg/mL) compared to group 1 (10.0, 10.0–10.0 pg/mL; $P < .001$) and group 2b (10.0, 10.0–570 pg/mL; $P = .010$) for samples of laboratories B and C. No significant difference was found between group 1 and group 2b. The cut-off value for detection of primary myocardial damage was 10.5 pg/mL (AUC: 0.71; 0.95% CI: 0.55–0.88; $P = .019$). However, a low sensitivity was found (42.9%; specificity: 100%). No significant ($P = .361$) cut-off value for secondary myocardial disease could be determined. The cTnT concentrations of the 6 healthy horses which were analyzed in both laboratories all were below the LOD of laboratories B (10.0 pg/mL) and C (4.0 pg/mL).

When only samples analyzed in laboratory C ($n = 58$) were considered, the median cTnT was 4.0 pg/mL (range, 4.0–6.0 pg/mL) in healthy horses ($n = 20$) and a significantly higher ($P < .001$) cTnT concentration was found in horses with primary myocardial damage (42.2; 4.0–1,341.0 pg/mL). The median cTnT concentration in horses with primary myocardial damage also was

significantly higher ($P = .004$) than that in horses with secondary myocardial damage (4.0; 4.0–13.22 pg/mL). No significant difference was found between healthy horses or horses with secondary myocardial damage (Fig 2). Based on the ROC curve, a significant ($P = .001$) cut-off (6.6 pg/mL) could be determined for detection of primary myocardial damage (AUC: 0.89; 95% CI: 0.78–1.00; sensitivity: 81%; specificity: 100%).

Comparison of cTnI and cTnT Values

A significant correlation between log cTnI and log cTnT was found (Fig 4). The Spearman correlation coefficient between the cTnI and hs-cTnT concentrations was 0.621 ($P = .01$). Thirty-six of all samples had a cTnI value above the cut-off.

When only samples analyzed in laboratory C were considered, the Spearman correlation coefficient between the cTnI and hs-cTnT assays increased to 0.801. The AUC was not significantly different between the cTnI and the cTnT ROC curves ($P = .376$). Twenty-three of the 58 samples had a cTnT concentration above the cut-off (6.6 pg/mL, Table 1). Four horses were positive for myocardial damage based on the cTnI results, whereas the cTnT concentration was below the cut-off. Three of these horses had atypical myopathy and the last horse had severe mitral valve regurgitation with atrial dilatation caused by rupture of the chordae tendineae. Two horses had high cTnT concentrations with normal cTnI concentrations of which 1 had severe aortic regurgitation and the other atypical myopathy.

Discussion

Cardiac troponin I is routinely used in equine clinical practice, but different assays produce different results. No such variations exist for cTnT assays because only 1 manufacturer produces these assays. For this reason, a number of laboratories in human medicine might switch from cTnI to the new hs-cTnT assay for detection of cardiac disease, which might decrease the availability of cTnI measurement in clinical practice.¹⁴ Because limited information about cTnT is available in horses,^{15,16} the aim of this study was to compare cTnI and cTnT concentrations in horses with and without cardiac disease.

Cardiac troponin I was measured with the Access Accu assay in 1 laboratory (laboratory A). Measurement of cTnT was performed in 2 laboratories (B and C) with the LOD set at 10.0 pg/mL and 4.0 pg/mL in laboratories B and C, respectively (Fig 1). Reference results for cTnI and cTnT were obtained by blood sample analysis of healthy horses and, for both cTnI and cTnT, a significant difference was found between the healthy horses and those with primary myocardial damage. An optimal cut-off value could be established for both cTnI and cTnT. In a previous study, an older, less sensitive cTnT assay was used with an LOD of 40 pg/mL.¹⁵ All healthy horses had a cTnT concentration under this LOD. However, in our study, a 10-fold more sensitive cTnT assay was used and showed that the

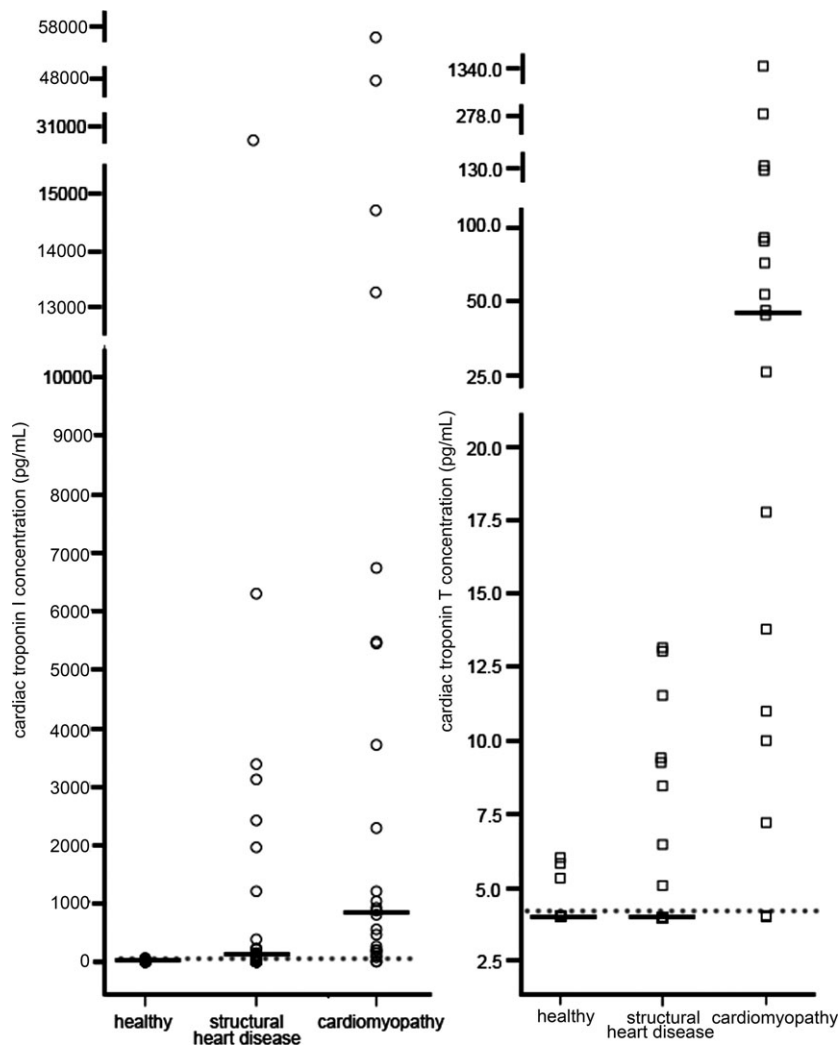


Fig 2. Comparison of the log cardiac troponin I ($n = 99$, laboratory A) and T ($n = 58$, laboratory C) concentration in healthy horses (group 1), horses with primary myocardial damage (group 2a), and horses with secondary myocardial damage caused by structural heart disease (group 2b). The cut-off concentration is demonstrated by the horizontal dotted line. The median troponin concentration within each group is indicated by a black horizontal bar.

cTnT concentration in healthy horses was much lower than 40 pg/mL. Although an optimal cut-off concentration for primary myocardial disease was established, sensitivity was low when the LOD of both laboratories B and C was set at 10.0 pg/mL. However, when only samples analyzed at laboratory C were included with the LOD set at 4.0 pg/mL, the optimal cut-off was lower and the AUC of the cTnT assay approached the AUC of the cTnI assay. This cTnT cut-off concentration provided similar results to categorize horses in different groups as the cTnI cut-off concentration (Table 1). Therefore, cTnI and cTnT both were able to differentiate healthy horses from horses with primary myocardial damage.

Although a significant correlation between cTnI and cTnT was found (Fig 4), quantitative differences existed: the optimal cTnI cut-off concentration for primary myocardial disease (0.095 ng/mL or 95 pg/mL) was more than 10 times higher than the cTnT cut-off concentration (6.6 pg/mL). Because qualitative results

are comparable (Table 1), the quantitative assay difference seems less important for diagnosis of myocardial damage and only demonstrates that the same assay has to be used if troponins are reanalyzed for patient re-evaluation.

Similar to the situation in human medicine, it seems that the diagnostic efficacy of cTnI and cTnT is comparable in horses.³ In our study, 4 horses had high cTnI concentrations, whereas the cTnT assay result was low: 3 of these horses had atypical myopathy, whereas the other horse had severe valvular regurgitation. Conversely, 2 horses had high cTnT concentrations with a low cTnI concentration. Because extensive postmortem examination was not performed on the horses that were determined to be clinically normal with either test, it could not be determined whether cTnI or cTnT performed better to detect cardiac disease.

Despite the good sensitivity of the hs-cTnT assay, the LOD was set at 10.0 pg/mL in laboratory B and 4.0 pg/mL in laboratory C. According to laboratory B,

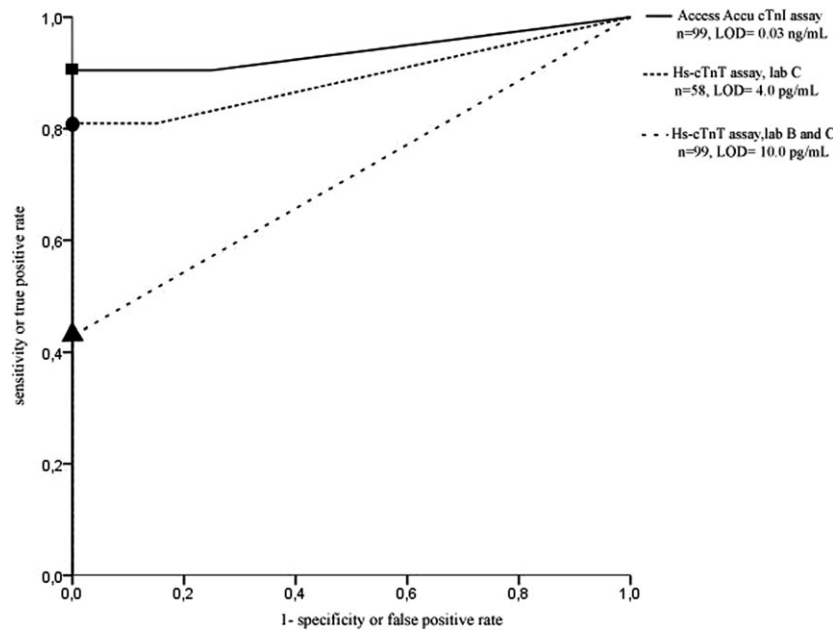


Fig 3. Receiver operator characteristic (ROC) curve of the Access Accu troponin I (cTnI) assay of laboratory A (■ cut-off = 0.095 ng/mL), the high-sensitive troponin T (cTnT) assay of laboratory B and C together (● cut-off = 10.5 pg/mL) and of laboratory C separately (▲ cut-off = 6.6 pg/mL) for detection of primary myocardial damage.

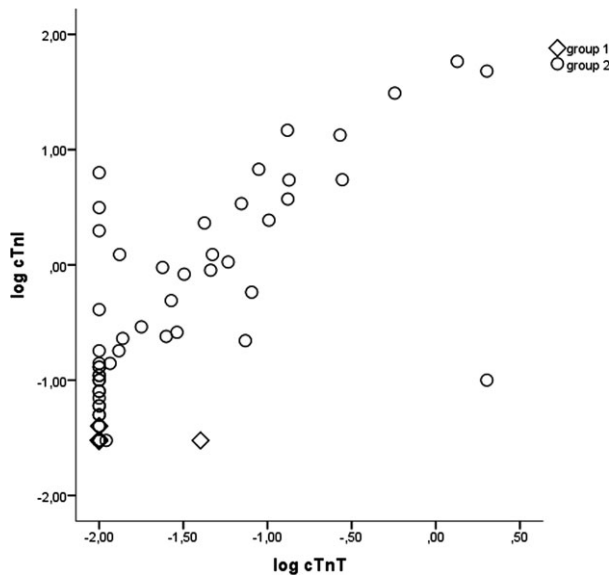


Fig 4. A significant correlation ($r = 0.621$) between the log troponin I value of the Access Accu cardiac troponin I assay and the log troponin T value of the high-sensitive troponin T assay of horses of group 2 was found ($P = .01$).

this higher LOD was chosen as a safety margin. In human medical practice, cardiac troponins are mostly measured for the early diagnosis of myocardial infarction. One benefit of high-sensitive assays is their improved diagnostic accuracy in the case of early presentation of patients with chest pain. Patients with a cTnT concentration above the 99th percentile of a large reference population are diagnosed with acute myocardial infarction and a hs-cTnT cut-off concentration of

Table 1. Cross-tabulation comparing the high-sensitive troponin T assay of laboratory C (cut-off: 6.6 pg/mL, limit of detection: 4.0 pg/mL) and the Access Accu troponin I assay of laboratory A (cut-off: 0.095 ng/mL, limit of detection: 0.03 ng/mL) for detection of myocardial disease.

	hs-cTnT		Total
	Negative	Positive	
cTnI			
Negative	31 (53%)	2 (3%)	33 (57%)
Positive	4 (7%)	21 (36%)	25 (43%)
Total	35 (60%)	23 (40%)	58 (100%)

hs-cTnT, high-sensitive cardiac troponin T; cTnI, troponin I.

14.0 pg/mL has been determined.²² Therefore, even with an LOD of 10.0 pg/mL, the hs-cTnT assay still is useful for detection of myocardial injury in human patients. However, myocardial infarction is very rare in equine medicine and valvular heart disease is most commonly diagnosed.²³ Of a total of 555 horses with various cardiac diseases, Gehlen et al²⁴ diagnosed valvular heart disease in approximately 65% of the patients. In our study, most of the horses with suspected primary myocardial damage ($n = 23$), such as myocarditis or atypical myopathy because of *Acer pseudoplatanus* intoxication, had cTnI (0.90 ng/mL, 0.03–58.27) and cTnT (42.2 pg/mL, 4.0–1,341.0) concentrations that were well above the established cut-off concentrations. Horses with secondary myocardial disease caused by structural heart disease had significantly lower cTnI and cTnT concentrations. No significant cut-off concentration for structural heart disease could be determined. However, the

cTnI concentration in horses with secondary myocardial damage was significantly higher than that in healthy horses. Thus, horses with structural heart disease also could have minor increases in troponin concentrations. Two of the 3 horses with aortopulmonary fistulas had acute clinical signs and a cTnI increase (0.26 and 1.98 ng/mL) of greater extent than most of the other horses in group 2b. In contrast to valvular heart disease, aortopulmonary fistulation often is an acute event, which might cause a sudden and extensive release of cTnI.

One limitation of our study was that not all cTnT samples could be analyzed at the same laboratory. Not only the LOD but also other laboratory characteristics could have influenced results. A large study in which the same samples are analyzed with the same assay in different laboratories could elucidate variation among laboratories. Samples for cTnI and cTnT also were not analyzed at the same time. However, all samples were stored at -20°C , analyzed within the time recommended by the manufacturer, and only thawed once. CTnT is known to be stable for 3 months at -20°C and only 9/99 samples were stored >3 months (maximum 5.5 months). Therefore, the influence of storage on our results is most likely minimal.²⁵ Thirdly, it could be argued that extensive muscle damage caused troponin increase in horses with atypical myopathy. However, skeletal muscle damage has no impact on cTnI concentrations and only has an influence on first generation cTnT assays^{26,27} Cardiac damage in atypical myopathy previously has been identified by echocardiography, ECG, and necropsy findings^{19,20} and was thought to be the source of the troponin increase in our study. Finally, it could not be ruled out that the troponin increase in horses with structural heart disease was caused by additional primary myocardial damage. However, no myocardial abnormalities were seen in these horses during echocardiographic examination.

Conclusion

Both cTnI and cTnT can distinguish healthy horses from horses with myocardial disease and have comparable diagnostic value. However, absolute cTnI and cTnT differences exist, which indicates that the same assay should be used for patient re-evaluation.

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Conflict of Interest Declaration: The authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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Footnotes

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- ^a Roche Diagnostics GmbH, Indianapolis, IN
^b ELISA Troponin T, Boehringer, (Manheim, Germany), now Roche Diagnostics Corporation (Indianapolis, IN)
^c Engel Engineering Services GmbH, Offenbach, Germany
^d Cryovials 2 mL, VWR International, Leuven, Belgium
^e Beckman Coulter Inc, Fullerton, CA
^f Version 22.0, Chicago, IL
^g Version 13.2.0.0, Ostend, Belgium
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