



# Plasma homocysteine concentrations in healthy horses and horses with atrial fibrillation<sup>☆</sup>

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## KEYWORDS

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**Abstract** *Introduction:* Homocysteine (HCY) is an amino acid produced from methionine metabolism. Plasma homocysteine concentrations ( $[HCY]_p$ ) are elevated ( $>13 \mu\text{mol/L}$ ) in people with atrial fibrillation (AF) and can predict the recurrence of AF after cardioversion. This study aimed to validate a commercially available human HCY assay for use in horses to develop reference intervals for  $[HCY]_p$  and compare  $[HCY]_p$  in healthy horses and horses with AF. *Animals:* Healthy horses ( $n = 27$ ) and horses with AF ( $n = 55$ , 34 of which were cardioverted using transvenous electrical cardioversion).

<sup>☆</sup> A unique aspect of the Journal of Veterinary Cardiology is the emphasis of additional web-based materials permitting the detailing of procedures and diagnostics. These materials can be viewed (by those readers with subscription access) by going to <http://www.sciencedirect.com/science/journal/17602734>. The issue to be viewed is clicked and the available PDF and image downloading is available via the Summary Plus link. The supplementary material for a given article appears at the end of the page. To view the material is to go to <http://www.doi.org> and enter the doi number unique to this paper which is indicated at the end of the manuscript.

**Data presentation:** These data were presented as a poster at ECEIM congress, Helsinki, Finland in November 2016 and as a short presentation at the Annual Symposium of the Graduate School of Cellular and Biomedical Sciences, University of Bern in January 2017.

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**Materials and methods:** Blood samples were analysed for HCY using an automated enzyme-cycling assay (Homocysteine Cobas C, Integra, Roche) and creatinine (compensated Jaffe method). Assay linearity and precision were assessed, reference intervals calculated and [HCY]<sub>p</sub> and creatinine compared between groups.

**Results:** The assay was precise (coefficient of variation 1.6–4.3%, n = 10 repetitions) and provided linear results (r = 0.99 for spiked and natural samples) for a range of [HCY]<sub>p</sub>. The reference interval for [HCY]<sub>p</sub> was 1.5–7.8 μmol/L. The plasma concentration of homocysteine was 4.65 ± 1.5 μmol/L (mean ± standard deviation) in healthy horses and 4.65 ± 1.72 μmol/L in horses with AF (p=0.99); [HCY]<sub>p</sub> was not associated with recurrence of AF (n = 18, p=0.97). A weak, positive correlation between plasma creatinine and [HCY]<sub>p</sub> was detected (r = 0.295, p=0.008, r<sup>2</sup> = 0.11).

**Conclusions:** This assay allows precise measurement of [HCY]<sub>p</sub> in horses. Unlike in people, [HCY]<sub>p</sub> is not increased in horses with AF and cannot predict AF recurrence. This might be due to differences in the underlying pathological mechanisms of AF development in people and horses.

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### Abbreviations

AF	atrial fibrillation
[Creat] <sub>p</sub>	plasma concentration of creatinine
HCY	homocysteine
[HCY] <sub>p</sub>	plasma concentration of homocysteine
HHCY	hyperhomocysteinemia
LA	left atrial
NSR	normal sinus rhythm
QS	quinidine sulphate
TVEC	transvenous electrical cardioversion

### Introduction

Homocysteine (HCY), an amino acid produced from cellular metabolism of methionine, is an important biomarker of cardiovascular disease in humans [1]. Experimentally induced hyperhomocysteinemia (HHCY) is associated with structural and electrical myocardial remodelling through many pathways, including endothelial dysfunction, oxidative stress, vascular remodelling, nitric oxide synthase induction, matrix metalloproteinase and N-methyl D-aspartate receptor activation and interference with K<sup>+</sup> and Ca<sup>2+</sup> handling [1–3].

Several studies have shown that plasma concentrations of homocysteine ([HCY]<sub>p</sub>) are elevated in some people with nonvalvular atrial fibrillation (AF) and that preconversion [HCY]<sub>p</sub> > 13 μmol/L is associated with an increased risk of AF recurrence following successful conversion to normal sinus rhythm (NSR) [4–8].

Currently, predictors of AF recurrence in horses that have been successfully converted to

NSR are associated with historical information (duration of arrhythmia >4 months and previous episode of AF), echocardiographic abnormalities detected after successful conversion (presence of persistent left atrial (LA) stunning, mild-moderate mitral insufficiency, increased LA size indices) or electrophysiological characteristics (AF cycle length) [9–12]. In horses with ‘lone’ AF, the recurrence rate after treatment is reported between 15 and 40%, but it is higher in horses with >4 month duration of AF, mild or greater mitral regurgitation and in horses with a history of previous treatment for AF [10–12]. A reliable preconversion assessment of the risk of AF recurrence is difficult and relies heavily on the experience of the treating clinician. With the high costs and risks associated with treatment of AF, having a more accurate assessment of the risk of AF recurrence prior to treatment would be useful.

There is limited knowledge about [HCY]<sub>p</sub> in horses. Although the common lifestyle risk factors for HHCY in humans such as smoking, alcoholism or sedentary lifestyle are not transferable to equine practice, possible causes of HHCY in horses include dietary excess of methionine, genetic mutations within the methionine-homocysteine metabolism pathway, dietary deficiencies of folate, vitamin B<sub>2</sub>, B<sub>6</sub> or B<sub>12</sub>, increasing age or concurrent renal disease. Plasma concentrations of HCY have been measured in horses using high-pressure liquid chromatography [13–17], but this method is costly, time consuming and not available in all laboratories. Reference intervals for healthy horses are not published, and no studies have been performed in horses with AF.

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