Journal of Feline Medicine and Surgery (2010) **12**, 904–909
doi:10.1016/j.jfms.2010.06.010

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jfms

Signs of left heart volume overload in severely anaemic cats

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Anaemia induces haemodynamic compensatory mechanisms resulting in volume overload and increased left heart dimensions in humans and dogs. The aims of this retrospective study were to investigate the effects of anaemia on echocardiographic left heart dimensions, vertebral heart size (VHS) and radiographic evidence of congestive heart failure (CHF) in cats. Fifteen cats fulfilled the inclusion criteria and were classified as mildly anaemic (haematocrit (Hct) > 18–24%) or severely anaemic (Hct ≤ 18%). Eight out of eight severely anaemic cats had left atrial enlargement compared with 1/6 mildly anaemic cats ($P < 0.005$) and severely anaemic cats also had a larger median left ventricular end-diastolic diameter (1.80 cm versus 1.27 cm, respectively; $P < 0.05$). No difference was found between the groups in VHS or frequency of radiographic signs of CHF. Despite the small sample size, these preliminary findings suggest that severely anaemic cats are more likely to have enlarged left heart dimensions than mildly anaemic cats.

Date accepted: 22 June 2010

Anaemia results in a decrease in the oxygen-carrying capacity of the blood and, therefore, a reduction in tissue oxygenation, prompting a number of complex haemodynamic compensatory mechanisms.

In response to an acute decline in haemoglobin levels, generalised peripheral vasodilation occurs, predominantly due to increased nitric oxide activity.[1–3] An acute reduction in blood viscosity and later, recruitment of collateral circulation, also contribute to an overall reduction in systemic vascular resistance.[4–6] Cardiac afterload is thus reduced, promoting an increase in cardiac stroke volume and cardiac output, as described in both humans and dogs.[4,7] These acute responses are also sustained during chronic anaemia[9,11] and the increased cardiac output does not resolve immediately following correction of the anaemia.[4]

Peripheral vasodilation results in a tendency towards 'arterial under-filling'.[8] This results in activation of neuroendocrine compensatory mechanisms to promote renal sodium and water retention. Such mechanisms have been described in chronic anaemia in humans and experimentally in dogs.[9,11] The neuroendocrine responses involved include activation of the renin–angiotensin–aldosterone system, increased sympathetic activity and the non-osmotic release of arginine vasopressin.[11] The time-scale of these neuroendocrine responses is difficult to determine precisely. It is thought that activation of the renin–angiotensin–aldosterone system and increased sympathetic activity occur rapidly in response to a reduction in peripheral vascular resistance.[8] Sustained activation of these mechanisms has been documented in chronic anaemia in humans.[11] Increased intravascular volume stimulates the release of atrial natriuretic peptide (ANP), itself a mediator of vasodilation, later in the course of disease.[12]

Chronic anaemia can lead to progressive circulatory volume overload, by the mechanisms described above. In humans and dogs, it has been shown that the increase in cardiac preload leads to increased left ventricular end-diastolic volume and in time, this volume overload can induce eccentric left ventricular hypertrophy.[9,13,14]

Anaemia is a common presenting complaint of cats. However, little work has been performed in cats to investigate the association between anaemia and cardiovascular changes. One published case report described cardiomegaly in a kitten with anaemia secondary to flea infestation, with subsequent resolution

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1098-612X/10/120904+06 $36.00/0

of the cardiomegaly following normalisation of the haematocrit (Hct).[15]

We hypothesised that anaemia would cause neuroendocrine activation that would increase the likelihood of developing circulatory volume overload and that this would manifest as increased left atrial and left ventricular diastolic dimensions. We hypothesised that these cats would be at increased risk of congestive heart failure (CHF). We also hypothesised that left heart enlargement would be greater in cats with severe anaemia compared with mild anaemia. The aims of this study were to compare left heart dimensions in mildly versus severely anaemic cats, to compare vertebral heart size (VHS) and to compare the proportion of cats with radiographic changes consistent with CHF in each group.

Materials and methods

Case selection

Electronic medical records of cats admitted to the Royal Veterinary College, Queen Mother Hospital for Animals (QMHA), between January 2003 and December 2008 were reviewed by using over 40 different search terms. Cats were identified with anaemia on presentation, as defined by a Hct $< 24\%$ (normal reference interval 24–45%).

Inclusion criteria were age >6 months, anaemia of any aetiology >24 h duration (other than traumatic blood loss) and echocardiographic records. Cats were excluded if they had received isotonic crystalloid fluids at a rate greater than 4 ml/kg/h, natural or synthetic blood products, or any other colloid solution following detection of anaemia and prior to echocardiography, to exclude the likelihood of iatrogenic volume overload.[23] Additional exclusion criteria included previously diagnosed cardiac disease, left ventricular end-diastolic septal or free wall thickness ≥6 mm, evidence of hyperthyroidism and systemic hypertension (defined as non-invasive systolic blood pressure >180 mmHg measured by Doppler sphygmomanometry), documented either previously or currently.

Cats which met the inclusion criteria were further classified as having mild or severe anaemia according to Hct, with mild anaemia defined as >18–24% and severe anaemia ≤18%.

Recorded variables

Variables recorded in all cats included signalment, Hct on initial presentation, presence or absence of regenerative anaemia (defined as an absolute aggregate reticulocyte count $>40 \times 10^9$/l), aetiology of the anaemia and echocardiographic left heart dimensions. Where thoracic radiographs were available, these were reviewed by both a board-certified cardiologist and a board-certified radiologist blinded to the details of each case. Additional variables recorded in these cats included VHS and whether radiographic changes were present which were consistent with CHF (pleural effusion or pulmonary oedema). VHS was considered to be normal at ≤8.5 vertebrae (v).[16,17] Both observers made an independent assessment and then a consensus was reached if opinions initially differed.

The echocardiographic variables were obtained from patient records. All echocardiograms were recorded on a GE Vivid-7 by either a board-certified cardiologist or a cardiology resident. Variables recorded included 2D left atrial end-systolic diameter (LAD) in a right parasternal long axis view; 2D diastolic left atrial to aortic ratio (LA:Ao) in short-axis and M-mode left ventricular end-diastolic diameter (LVDd).

We defined left heart volume overload as the presence of any of the following criteria: LAD > 1.6 cm,[18,19] LA:Ao > 1.5,[20,21] or LVDd > 2.0 cm.[22]

Statistical methods

All analyses were performed using computerised statistical analysis software (GraphPad Prism 5.00, GraphPad Software, San Diego, CA, USA, 2007). Differences in categorical data (presence or absence of left heart volume overload or CHF) between cats with mild and severe anaemia were analysed using the Fisher's exact test. Continuous data were compared using the Mann Whitney U test. Statistical significance was set at $P < 0.05$.

Results

Of 6123 cats admitted to the QMHA during the study period, 15 were identified which fulfilled all the inclusion criteria. Breeds represented were domestic shorthair ($n = 8$), domestic longhair ($n = 2$), British Blue ($n = 2$), British Shorthair ($n = 1$), European Shorthair ($n = 1$) and Balinese ($n = 1$). All cats were neutered with 11 males and 4 females. Ages ranged from 17 months to 15 years (median age 9 years).

The aetiology of the anaemia was identified in 12/15 cats and categorised as follows: immune-mediated haemolytic anaemia (IMHA, $n = 5$), renal insufficiency ($n = 5$), myelodysplasia ($n = 1$) and pyothorax ($n = 1$). Seven cats had mild anaemia, all of which were non-regenerative. Eight cats had severe anaemia, of which three were non-regenerative and five were regenerative. All of the cats with renal insufficiency had mild anaemia and all cats with IMHA had severe anaemia.

Left atrial measurements were not available for one cat. Median LAD was increased in severely anaemic cats (1.77 cm), compared with mildly anaemic cats (1.48 cm; $P < 0.05$, Fig 1), with 8/8 severely anaemic cats having LAD > 1.6 cm, versus only 1/6 mildly anaemic cats ($P < 0.005$). However, although there was a trend towards an increased median LA:Ao in severely anaemic cats (1.57) compared with mildly anaemic cats (1.26), this difference did not reach statistical significance ($P = 0.093$, Fig 2). None of the six mildly anaemic cats had LA:Ao > 1.5, compared

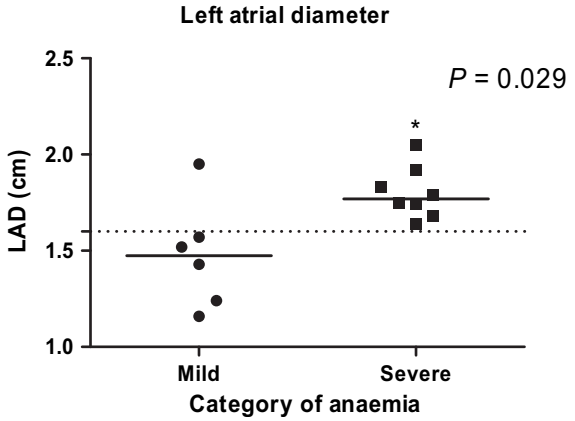

Fig 1. Scatter dot plot of LAD (values in cm) in mild and severe anaemia groups. The solid lines denote the median values. LAD was significantly larger in severely anaemic cats, all of which exceeded the upper limits of normal (1.6 cm; denoted by dotted line).

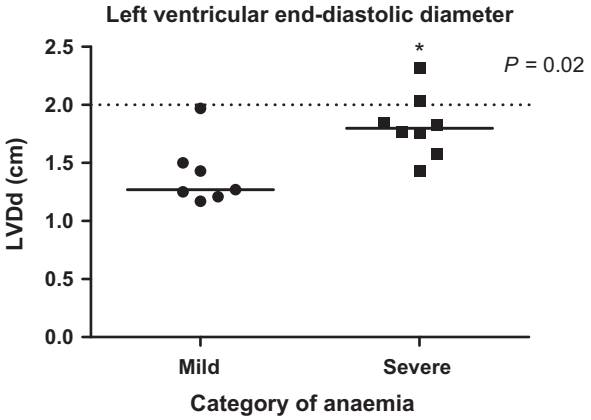

Fig 3. Scatter dot plot of LVDd (values in cm) in mild and severe anaemia groups. The solid lines denote the median values. LVDd was larger in severely anaemic than mildly anaemic cats but did not exceed normal limits (2 cm; denoted by dotted line) in either group.

with 4/8 severely anaemic cats ($P = 0.085$). Median LVDd was greater in severely anaemic cats (1.80 cm) compared with mildly anaemic cats (1.27 cm, $P < 0.05$, Fig 3), with 2/8 severely anaemic cats having LVDd > 2.0 cm, versus 0/7 mildly anaemic cats ($P = 0.467$). All eight cats with severe anaemia had at least one criterion for left heart volume overload compared with only 1/7 cats with mild anaemia ($P = 0.001$).

Thoracic radiographs were available for review in 12 of the cases; five mildly anaemic cats and seven severely anaemic cats. Median VHS of severely anaemic cats was 9.1 vertebral bodies, compared with 8.2 vertebral bodies in mildly anaemic cats ($P = 0.088$, Fig 4). Both observers agreed with respect to the presence or absence of radiographic changes consistent with CHF in all cases; one cat was excluded due to poor quality radiographs. Five out of seven severely anaemic cats and 2/4 mildly anaemic cats had radiographic changes consistent with CHF (odds ratio 2.5, 95% confidence interval 0.33–42.5; $P = 0.576$, Table 1).

Discussion

The results of this retrospective study suggest that severely anaemic cats are more likely to have increased left heart dimensions than mildly anaemic cats. This is consistent with findings in anaemic human patients, where the mechanism is believed to be associated with neuroendocrine compensatory responses such as activation of the renin–angiotensin–aldosterone system, resulting in sodium and water retention and leading to volume overload.[10,11] Such mechanisms

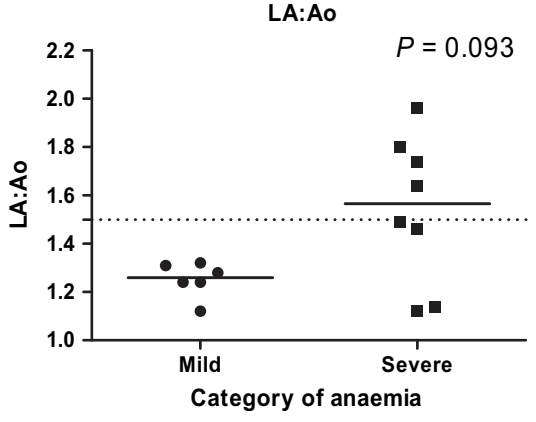

Fig 2. Scatter dot plot of LA:Ao in mild and severe anaemia groups. The solid lines denote the median values. Median LA:Ao exceeds the upper limit of normal (1.5; denoted by the dotted line) in severely anaemic, but not in mildly anaemic cats. The distribution of LA:Ao is much wider in severely, compared with mildly anaemic cats.

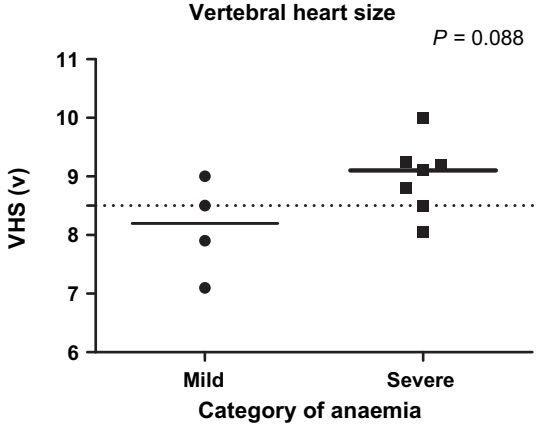

Fig 4. Scatter dot plot of VHS (values in vertebrae) in mild and severe anaemia groups. The solid lines denote the median values. Median VHS exceeded the upper limit of normal (8.5 v; denoted by the dotted line) in severely anaemic, but not in mildly anaemic cats.

Table 1. Echocardiographic indices of left heart dimensions, VHS and radiographic changes consistent with CHF in mildly and severely anaemic cats. Data are expressed as median (range).

Variable	Mild anaemia	Severe anaemia	*P* value
LAD	1.48 (1.16–1.95)	1.77 (1.64–2.05)	0.029
LA:Ao	1.26 (1.12–1.32)	1.57 (1.12–1.96)	0.093
LVDd	1.27 (1.17–1.97)	1.80 (1.43–2.32)	0.020
VHS	8.20 (7.10–9.00)	9.10 (8.05–10.00)	0.088
CHF_{rad}	2/4	5/7	0.576

CHF_{rad} = radiographic evidence of CHF, expressed as a proportion of cats for which radiographs were available for review. Significance was set at $P < 0.05$.

are prompted by a reduction in systemic vascular resistance in response to anaemia.[1–7]

All of the indices of volume overload were greater in the severely anaemic cats, but not all variables reached statistical significance. Despite review of a large number of records, very few cats met the study inclusion criteria as many anaemic cats had received blood products or other intravenous fluids prior to echocardiography. As a result, sample numbers were small and confidence intervals were wide. A difference in some of the criteria for volume overload was nonetheless still evident between cats with mild and severe anaemia. In this respect, it is interesting that LAD was significantly increased in severely anaemic cats but LA:Ao was not, suggesting that LAD is a more sensitive indicator of left atrial enlargement than LA:Ao in cats. In contrast, a previous study of left atrial sizes in cats receiving various fluid rates found that LAD and LA:Ao both increased in cats on a high intravenous fluid rate (10 ml/kg/h) and both decreased in cats which were volume-depleted.[23]

Left ventricular eccentric hypertrophy in response to chronic anaemia has been reported in both humans[14] and dogs[9] and results in increased LVDd with normal wall thickness. Cats with severe anaemia in our study had increased LVDd compared with mildly anaemic cats, although LVDd did not meet our criterion for volume overload in all but two severely anaemic cats. We chose to define normal LVDd as <2.0 cm, although values ≤1.8 cm have been used elsewhere.[22,24–26] We were not able to specifically investigate the effects of anaemia on left ventricular wall thickness, as we deliberately excluded cats with diastolic wall thickness ≥6 mm in order to prevent inclusion of cats with pre-existing hypertrophic cardiomyopathy.

Although not statistically significant, there was a trend for VHS to be greater in the severely anaemic cats (median 9.10 v compared with 8.2 v; Table 1). Very few cats had thoracic radiographs available, including only four of the mildly anaemic cats. Changes consistent with CHF were present in 2/4 of the mildly anaemic cats and 5/7 of the severely anaemic cats for which radiographs were available for review. Larger numbers of cats in each group would be necessary to test the association between anaemia and radiographic signs of CHF. Not all cats in this study with radiographically suggestive changes may have actually had CHF, because other diseases can produce similar findings of pulmonary infiltrates and pleural effusion. Compared with VHS, echocardiography is a more accurate diagnostic tool for detecting small changes in cardiac chamber size.

Although the findings of this study are suggestive of volume overload, there are other possible causes of left heart enlargement, such as myocardial disease, systolic dysfunction, dysrhythmias or congenital heart disease.[27,28] However, these conditions would have been readily diagnosed with echocardiography and concurrent electrocardiographic recording, making excessive plasma volume expansion a more likely explanation in the cats described here. By excluding cats with a history of receiving blood products or high fluid rates, we believe the evidence of left heart dilation found in some cats was most likely associated with the underlying disease process responsible for the anaemia, rather than with intravenous fluid therapy.

The development of cardiovascular signs associated with anaemia in humans depends on the severity of the anaemia, its rate of onset and the presence and nature of any pre-existing cardiac disorders.[29] It was not possible to document the rate of onset or duration of anaemia in cats prior to presentation in this study, thus it cannot be determined whether the degree of left cardiac chamber enlargement is related purely to the severity of anaemia, or if the duration and rate of development are also risk factors. Additionally, we were not able to confirm the precise pathophysiological mechanisms for the association between the apparent volume overload and severe anaemia in the cats reported here, but it is likely that they are the same as those reported in anaemic human patients.

We used mildly anaemic cats as a control group to limit confounding factors associated with the underlying causes of anaemia. There were still differences in the frequency of underlying conditions, perhaps reflecting the likelihood of some diseases to cause either severe or mild anaemia. However, normal healthy cats would have been a less satisfactory control group and would offer no advantage over normal echocardiographic and radiographic reference intervals.

This study measured anaemia based on Hct rather than a manual packed cell volume (PCV), as PCV measurements were not available in all cats. The Hct is an automated reading and can be erroneous for a number of reasons, such as under-filling of an ethylenediamine tetra-acetic acid (EDTA) tube following sample collection. Conversely, a manual PCV can be erroneous due to operator-error. The same haematology machine was used throughout for all samples, thus reducing inter-sample variability. In those cats where both Hct and PCV were available, the values

were consistently related, thus it is unlikely that the use of Hct value has significantly affected the results of this study.

Hydration status has been shown to affect echocardiographic chamber measurements, with a mean body weight reduction of 5% producing significant decreases in LAD and LA:Ao.[23] We excluded cats which may have been at risk for iatrogenic volume overload (those which had received crystalloid fluid therapy at a rate greater than 4 ml/kg/h or had received colloids) but did not account for cats which may have been dehydrated on presentation. This is a confounding factor which could be eliminated in a prospective study.

The number of cats studied was small, but our preliminary findings suggest that cats with severe anaemia are more likely to have an increased LAD and LVDd, compared with mildly anaemic cats. We suggest that these findings represent an increased intravascular volume due to haemodynamic compensatory mechanisms and that fluid therapy should be approached with caution in these cats, as they are more likely to be susceptible to CHF. We hypothesise that cats presenting with anaemia and findings consistent with volume overload will benefit from treatment of their anaemia to reduce neuroendocrine activation and the associated sodium and water retention. Therefore, blood transfusion should neither be avoided nor delayed in anaemic cats with changes consistent with volume overload and CHF.

Based on the preliminary results of this study, a larger, prospective trial is required, with measurements recorded prior to the administration of any fluids, in order to test these conclusions and confirm the risk of volume overload in severely anaemic cats. It would be useful to follow a cohort of anaemic cats over time, to investigate the effects of the duration of anaemia on the rate of development of volume overload and possible associated cardiac changes, such as left ventricular hypertrophy. Measurement of neuroendocrine markers would also be valuable, to assess the possible contribution of such mechanisms to the cardiovascular changes observed. However, investigation of the effects of feline anaemia on the cardiovascular system over time is likely to be limited by the poor prognosis and short life-expectancy associated with many of the underlying diseases in our feline patients.

Acknowledgements

The authors would like to thank Charlotte Pace for her help with data collection, Chris Lamb for his help and the clinicians and referring veterinary surgeons who managed the cases reported here.

References

1. Anand IS, Chandrashekhar Y, Wander GS, Chawla LS. Endothelium-derived relaxing factor is important in mediating the high output state in chronic severe anemia. *J Am Coll Cardiol* 1995; **25**: 1402–7.
2. Martin W, Smith JA, White DG. The mechanisms by which haemoglobin inhibits the relaxation of rabbit aorta induced by nitrovasodilators, nitric oxide, or bovine retractor penis inhibitory factor. *Br J Pharmacol* 1986; **89**: 563–71.
3. Anand IS, Florea VG. High output cardiac failure. *Curr Treat Options Cardiovasc Med* 2001; **3**: 151–9.
4. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. *Am Heart J* 1972; **83**: 415–26.
5. Fowler NO, Holmes JC. Blood viscosity and cardiac output in acute experimental anemia. *J Appl Physiol* 1975; **39**: 453–6.
6. Martin C, Yu AY, Jiang BH, et al. Cardiac hypertrophy in chronically anemic fetal sheep: increased vascularization is associated with increased myocardial expression of vascular endothelial growth factor and hypoxia-inducible factor 1. *Am J Obstet Gynecol* 1998; **178**: 527–34.
7. Chamorro G, Rodriguez JA, Dzindzio B, Rapaport E. Effect of acute isovolemic anemia on cardiac output and estimated hepatic blood flow in the conscious dog. *Circ Res* 1973; **32**: 530–5.
8. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med* 1999; **341**: 577–85.
9. Levine HJ, Wolk MJ, Keefe JF, Bing OH, Snow JA, Messer JV. Myocardial mechanics and energetics in experimental iron-deficiency anemia. *Am J Physiol* 1977; **232**: H470–7.
10. Silverberg DS, Wexler D, Iaina A. The role of anemia in the progression of congestive heart failure. Is there a place for erythropoietin and intravenous iron? *J Nephrol* 2004; **17**: 749–61.
11. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson PA, Harris PC. Pathogenesis of oedema in chronic severe anaemia: studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. *Br Heart J* 1993; **70**: 357–62.
12. Nichols WW, Epstein BJ. Actions of selected cardiovascular hormones on arterial stiffness and wave reflections. *Curr Pharm Des* 2009; **15**: 304–20.
13. Bahl VK, Malhotra OP, Kumar D, et al. Noninvasive assessment of systolic and diastolic left ventricular function in patients with chronic severe anemia: a combined M-mode, two-dimensional, and Doppler echocardiographic study. *Am Heart J* 1992; **124**: 1516–23.
14. Aessopos A, Deftereos S, Farmakis D, et al. Cardiovascular adaptation to chronic anemia in the elderly: an echocardiographic study. *Clin Invest Med* 2004; **27**: 265–73.
15. Yaphe W, Giovengo S, Moise NS. Severe cardiomegaly secondary to anemia in a kitten. *J Am Vet Med Assoc* 1993; **202**: 961–4.
16. Buchanan JW. Vertebral scale system to measure heart size in radiographs. *Vet Clin North Am Small Anim Pract* 2000; **30**: 379–93, vii.
17. Litster AL, Buchanan JW. Vertebral scale system to measure heart size in radiographs of cats. *J Am Vet Med Assoc* 2000; **216**: 210–4.
18. Moise NS, Dietze AE, Mezza LE, Strickland D, Erb HN, Edwards NJ. Echocardiography, electrocardiography, and radiography of cats with dilatation cardiomyopathy, hypertrophic cardiomyopathy, and hyperthyroidism. *Am J Vet Res* 1986; **47**: 1476–86.
19. Schober KE, Maerz I, Ludewig E, Stern JA. Diagnostic accuracy of electrocardiography and thoracic radiography in the assessment of left atrial size in cats:

comparison with transthoracic 2-dimensional echocardiography. *J Vet Intern Med* 2007; **21**: 709–18.
20. Connolly DJ, Brodbelt DC, Copeland H, Collins S, Fuentes VL. Assessment of the diagnostic accuracy of circulating cardiac troponin I concentration to distinguish between cats with cardiac and non-cardiac causes of respiratory distress. *J Vet Cardiol* 2009; **11**: 71–8.
21. Abbott JA, MacLean HN. Two-dimensional echocardiographic assessment of the feline left atrium. *J Vet Intern Med* 2006; **20**: 111–9.
22. Adin DB, Diley-Poston L. Papillary muscle measurements in cats with normal echocardiograms and cats with concentric left ventricular hypertrophy. *J Vet Intern Med* 2007; **21**: 737–41.
23. Campbell FE, Kittleson MD. The effect of hydration status on the echocardiographic measurements of normal cats. *J Vet Intern Med* 2007; **21**: 1008–15.
24. Pipers FS, Hamlin RL. Clinical use of echocardiography in the domestic cat. *J Am Vet Med Assoc* 1980; **176**: 57–61.
25. Sisson DD, Knight DH, Helinski C, et al. Plasma taurine concentrations and M-mode echocardiographic measures in healthy cats and in cats with dilated cardiomyopathy. *J Vet Intern Med* 1991; **5**: 232–8.
26. Nyland TGMJ. Small animal diagnostic ultrasound. 2nd edn. Philadelphia: WB Saunders, 2002.
27. Katz A. Heart failure. Physiology of the heart. 4th edn. Philadelphia: Lippincott WIlliams and Wilkins, 2006: 546–83.
28. Apostolakis E, Shuhaiber JH. The surgical management of giant left atrium. *Eur J Cardiothorac Surg* 2008; **33**: 182–90.
29. Horl WH, Ertl G. Anaemia and the heart. *Eur J Clin Invest* 2005; **35**(suppl 3): 20–5.