

## Effects of Inter- and Intra-Observer Variability on Echocardiographic Measurements in Awake Cats

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### Summary

The objective of this study was to determine intra- and inter-observer variability of echocardiographic measurements in awake cats. Four observers with different levels of experience in echocardiography performed 96 echocardiographic examinations in four cats on four different days over a 3-week period. The examinations were randomized and blinded. The maximum within-day and between-day CV values were 17.4 and 18.5% for inter-ventricular septal thickness in diastole, 18.7 and 22.6% for left ventricular free-wall thickness in diastole, 9.8 and 14.9% for left ventricular end-diastolic diameter, 20.8 and 15.2% for left ventricular end-systolic diameter, and 21.2 and 18.4% for left ventricular shortening fraction. The maximum within-day CV values were most often associated with the least competent observer (i.e. the graduate student) and, the minimum CV values with the most competent observer (i.e. the associate professor in cardiology). A significant interaction between cat and observer was also evidenced. Thus, the most competent observer could not be replaced by any of the other observers.

### Introduction

Echocardiography is a well-established technique for the qualitative description of cardiac abnormalities and the quantitative assessment of heart anatomy and function. Measurements of atrial and ventricular sizes, ventricular thickness, and calculation of the shortening fraction (SF) were first reported in cats in 1979 (Pipers et al., 1979). The utility of such measurements has been particularly well illustrated in cats with dilated and hypertrophic cardiomyopathy (HCM) (Soderberg et al., 1983; Moise et al., 1986a; Sisson et al., 1991). Pathological hypertrophy in the cat is defined as a diastolic left ventricular free wall or septal thickness greater than 6 mm (Fox et al., 1995). There is also a current trend to increase the use of quantitative echocardiography in cats for the long-term follow-up of cardiac diseases, and especially as critical endpoints in drug efficacy trials. Repeated measurements overtime, for example, have been performed to assess the efficacy of diltiazem (Bright et al., 1991), enalapril (Rush et al., 1998), benazepril (Amberger et al., 1999) and

amlodipine (Snyder et al., 2001) in cats with HCM or systemic hypertension.

A prerequisite to the long-term follow-up of echocardiographic parameters in cats consists of standardization and validation of the echocardiographic examination. A standardized method for feline echocardiography has been described and normal values established (Allen, 1982; Soderberg et al., 1983; Fox et al., 1985; Moise et al., 1986a). Validation, however, still represents a challenge because of both cat- and observer-dependent factors. The small size of the feline heart results in suboptimal images causing frequent errors in measurement and interpretation (Moise and Fox, 1999). The accuracy of echocardiography has been studied for septal and left ventricular wall thickness during systole (Moise et al., 1986b) but, paradoxically, very little information is currently available on repeatability and reproducibility. In a study performed in 1985, the cats were anaesthetized and all echocardiograms were read and recorded by the same person (Moise et al., 1986b). Similarly, in a more recent study on horses (Young and Scott, 1998), all the measurements were recorded by a single observer. However, to our knowledge, no study has been reported on the between-day intra-observer variability of echocardiographic measurements and the differences between different observers in cats.

The following questions need to be answered before quantitative echocardiography is used for the follow-up of feline patients: (i) What is the coefficient of variation of the measurements (in other words, is an increase of 0.5 or 1 mm, for example, meaningful in comparison with the value of the coefficient of variation of the technique used)? (ii) Should the same observer systematically monitor the same patient throughout the follow-up (in other words, is it feasible to switch from one observer to another)? (iii) Does the experience of the observer need to be great in order to guarantee small between-day and within-day variability (in other words, does the quality of the assessment differ between a graduate student, resident and specialist)? The aim of this study was to determine the within-day and between-day intra-observer variability of echocardiographic measurements in awake cats obtained by different observers with various levels of experience.

## Materials and Methods

### Animals

Four domestic short-haired cats (three neutered males and one entire female) were used. The animals were 1–18 years old. The males weighing between 5 and 6 kg and the female 2.6 kg. The three males were clinically healthy on the basis of clinical examination, routine haematology results and serum chemistry. The female and the oldest animal, had a previous history of systemic hypertension (treated with amlodipine, 0.6 mg once a day), but was normotensive at the time of the trial. The owner's consent for each animal was obtained before enrolment in the study. The phase of this work involving animals was carried out in Ecole Nationale Vétérinaire d'Alfort.

### Echocardiographic procedure

Each cat was taken to a different and unfamiliar room and separated from its owner during the examination period to mimic the conditions of normal practice. The animals were not sedated for the examination. They were gently restrained in the standing position. The fur was clipped between the right fourth and fifth intercostal spaces. Coupling gel was applied generously to this area. An echocardiographic examination was carried out using a 7.5–10 MHz mechanical sector transducer (AU3 partner; Esaote, Italy). All measurements were made directly from the television screen freeze-frame image and were timed. Calipers could be positioned several times by the observer to obtain the final measurement. Ventricular measurements were taken using 2D-guided M-mode on the right parasternal ventricular short-axis view (Thomas et al., 1993), according to the recommendations of the American Society of Echocardiography (Sahn et al., 1978). These measurements were right ventricular end-diastolic diameter (RVDD), left ventricular end-diastolic diameter (LVDD), left ventricular end-systolic diameter (LVSD), left ventricular free-wall thickness in diastole (LVFWD), left ventricular free-wall thickness in systole (LVFWS), inter-ventricular septal thickness in diastole (IVSD), and inter-ventricular septal thickness in systole (IVSS). The left ventricular shortening fraction (SF) was then calculated. Measurements of aorta size and left atrial dimension were obtained by 2D echography, using a short-axis right-sided parasternal view of the aortic valve (Thomas et al., 1993), where commissures of the cusps are visualized during diastole. The internal shortaxis diameter of the aorta (Ao) was measured along the commissure between the non-coronary and left coronary aortic valve cusps. The left atrium (LA) was measured using the same frame, in a line extending from and parallel to the commissure between the non-coronary and left coronary aortic valve cusps.

### Observers

Four observers with different experience in echocardiography performed the examinations. Observer 3 was an associate professor in cardiology and diplomate of the European College of Veterinary Internal Medicine (Cardiology). Observers 1, 2 and 4 had been trained by observer 3, to use the ultrasonographic system described in the present trial. Observer 1 was a resident in small animal internal medicine; observer 2 was a veterinarian with 1-year intensive training in echocardiography; and observer 4 was a graduate student and considered a

beginner in echocardiography (< 4 months of training). All the observers were familiar with the echocardiographic examination procedure.

### Within-day and between-day intra-observer variability

Ninety-six echocardiographic examinations were performed on four different days over a 3-week period. All the examinations for a given day were carried out within 3 h. Only three observers were involved on a given day and each of them performed eight examinations, separately assessing each cat at two different times. The order of echocardiographic examination of the cats was randomized and the observer was blinded to the echocardiographic examination so that the observer could take measurements with the calipers, but could not see the figures on the screen. A person other than an observer was responsible for collecting all data.

### Statistical analysis

A software (SYSTAT version 8.0, SPSS Inc., Chicago, IL, USA) was used for the analysis.

The following general linear model was used for each observer and each ultrasonographic measurement:

$$Y_{ijkl} = \mu + \text{Day}_j + \text{Cat}_k + (\text{Day} \times \text{Cat})_{jk} + \varepsilon_{ijkl}$$

where  $Y_{ijkl}$  was the  $l$ th value measured for Cat  $k$  on Day  $j$  by observer  $i$ ,  $\mu$  was the mean of the observed values,  $\text{Cat}_k$  was the differential effect of Cat  $k$ ,  $(\text{Day} \times \text{Cat})_{jk}$  the interaction term between Day and Cat, and  $\varepsilon_{ijkl}$  was the model error.

The SD of repeatability was determined from the residual SD of the previous model and the SD of reproducibility from the square root of the mean square of 'observer', using the following general model:

$$Y_{ijkl} = \mu + \text{Ob}_i + \text{Day}_j + \text{Cat}_k + (\text{Ob} \times \text{Cat})_{ik} + (\text{Day} \times \text{Cat})_{jk} + \varepsilon_{ijkl}$$

where  $Y_{ijkl}$  was the  $l$ th value measured for Cat  $k$  on Day  $j$  by observer  $i$ ,  $\mu$  was the mean of the observed values,  $\text{Ob}_i$  was the differential effect of observer  $i$ ,  $\text{Cat}_k$  was the differential effect of cat  $k$ ,  $(\text{Ob} \times \text{Cat})_{ik}$  was the interaction term between Observer and Cat,  $(\text{Day} \times \text{Cat})_{jk}$  the interaction term between Day and Cat, and  $\varepsilon_{ijkl}$  was the model error. Significance was set at  $P < 0.05$ .

The data from the amlodipine-treated cat were not included in the assessment of between-day variability to avoid confusion between this variability and possible variation overtime in the given parameter because of potential effects of treatment.

In this study, observer 3 was considered the reference observer to determine possible 'switchability' between observers. All the differences in mean measurements for a given cat on a given day (except day 2 on which observer 2 was not involved) between each observer and observer 3 were calculated and represented on a graph. These differences were obtained for IVSD and LVFWD only. It was assumed that because only one investigator in routine would carry out a complete echographic investigation in a given animal, if observer 3 could not be replaced by a given observer for just one echocardiographic parameter, then it would not be possible to replace observer 3 with this observer for the overall

echocardiographic examination. We therefore selected only IVSD and LVFWD, i.e. the two critical endpoints used to diagnose a pathological ventricular hypertrophy, and to monitor drug efficiency.

## Results

### Echocardiographic measurements

The mean values of each parameter obtained by the reference observer are presented in Table 1. The diseased cat showed a mild increase in LVFWS and a slight decrease in LVSD and LVDD compared with the healthy animals. The mean duration of all the echocardiographic measurements was 3.3, 3.8, 2.0 and 4.6 min for observers 1, 2, 3 and 4, respectively.

### Within-day and between-day variability

The SD for the within-day and between-day intra-observer variability of each ventricular measurement is given in Table 2. The ranges of CVs for within-day and between-day variability are given in Table 3.

### Effect of observer experience on within-day and between-day variability

The CVs of within-day variability for observer 3 were the lowest for IVSD, LVDD, LVSD, LVFWS and LA/Ao, and were never the highest value. In contrast, observer 4 had the

highest CV values for IVSD, LVDD, LVSD, SF, RVDD, IVSS, LVFWS and LA/Ao. The CVs of between-day variability for observer 3 were the lowest for LVFWD and LVDD, but the highest for RVDD and IVSS. In contrast, the reproducibility of observer 4 was the best for LVSD, SF, RVDD and LVFWS. The other observers gave similar results to observer 3.

### Switchability between observers

A significant interaction between cat and observer was observed for IVSD ( $P < 0.01$ ), LVDD ( $P < 0.05$ ) and LVFWD ( $P < 0.05$ ), but not for the other parameters. The differences in mean values obtained between each observer and observer 3 are given in Fig. 1 for IVSD and Fig. 2 for LVFWD. Visual inspection of each figure shows large fluctuations for all observers, which exceeded the SD value of observer 3, except for IVSD on day 1 for observer 2.

## Discussion

This study was designed to document both inter- and intra-observer variability for echocardiographic measurements in cats. The conditions of this trial were similar to those of long-term monitoring under clinical conditions: (i) the animals were owner's cats, (ii) they were not specially trained to tolerate the examination procedure or accustomed to the observers, (iii) they were not sedated or anaesthetized, (iv) the procedure

Echocardiographic parameters	Cats	
	Healthy ( $n = 3$ )	Diseased ( $n = 1$ )
Right ventricular end-diastolic diameter (mm)	2.8 ± 1.36	1.7 ± 0.59
Interventricular septal thickness in diastole (mm)	4.6 ± 0.67	5.4 ± 0.34
Left ventricular end-diastolic diameter (mm)	15.9 ± 2.40	10.5 ± 0.41
Left ventricular free-wall thickness in diastole (mm)	4.5 ± 0.73	5.2 ± 0.22
Interventricular septal thickness in systole (mm)	7.8 ± 1.17	7.8 ± 1.01
Left ventricular end-systolic diameter (mm)	7.3 ± 2.63	4.1 ± 0.60
Left ventricular free-wall thickness in systole (mm)	7.8 ± 1.05	9.2 ± 0.34
Shortening fraction (%)	54.9 ± 10.97	61.0 ± 6.40
Left atrium size/aorta diameter	0.9 ± 0.09	0.8 ± 0.06

Table 1. Mean ( $\pm$ SD) values of repeated measurements of echocardiographic parameters in four cats by the referential observer

Table 2. Within-day and between-day intra-observer standard deviations for measurement of echocardiographic parameters in three healthy and one sick cats. Each echocardiographic examination was performed twice a day on three different days on the three animals by each observer. Only the data from the three healthy cats were used to assess between-day variability

Variability	Observer	Echocardiographic measurements								
		IVSD	LVFWD	LVDD	LVSD	SF	RVDD	IVSS	LVFWS	LA/Ao
Intraday SD	1	1.0	0.6	1.1	0.8	4.7	0.8	0.8	0.6	0.09
	2	0.5	0.8	1.0	0.8	4.2	1.3	0.7	0.7	0.1
	3	0.5	0.6	1.0	0.8	6.0	0.8	1.1	0.6	0.08
	4	1.0	0.8	1.3	1.5	9.8	1.4	1.3	0.9	0.1
Interday SD	1	0.4	0.8	2.2	0.8	6.8	1.2	0.4	1.2	0.07
	2	0.8	0.9	1.0	1.3	8.6	1.4	0.9	0.7	0.01
	3	0.6	0.5	0.3	1.1	5.7	1.7	1.3	0.5	0.06
	4	0.5	1.1	0.6	0.6	2.7	0.9	1.2	0.4	0.2

IVSD, interventricular septal thickness in diastole (mm); LVFWD, left ventricular free-wall thickness in diastole (mm); LVDD, left ventricular end-diastolic diameter (mm); LVSD, left ventricular end-systolic diameter (mm); SF, shortening fraction (%); RVDD, right ventricular end-diastolic diameter (mm); IVSS, interventricular septal thickness in systole (mm); LVFWS, left ventricular free-wall thickness in systole (mm); LA/Ao, left atrium size/aorta diameter.

Table 3. Within-day and between-day intra-observer coefficients of variation (range in %) for measurement of echocardiographic parameters in three healthy and one sick cats. Each echocardiographic examination was performed twice a day on three different days on the four animals by each observer. Only the data from the three healthy cats were used for the assessment of between-day variability

Echocardiographic parameters	Variability (CV range)	
	Within-day	Between-day
Right ventricular end-diastolic diameter (mm)	30.1–38.1	36.7–61.9
Interventricular septal thickness in diastole (mm)	9.7–17.4	6.6–18.5
Left ventricular end-diastolic diameter (mm)	6.9–9.8	1.6–14.9
Left ventricular free-wall thickness in diastole (mm)	10.5–18.7	10.5–22.6
Interventricular septal thickness in systole (mm)	10.1–16.4	5.3–16.3
Left ventricular end-systolic diameter (mm)	11.1–20.8	7.3–15.2
Left ventricular free-wall thickness in systole (mm)	6.9–11.9	6.0–15.2
Shortening fraction (%)	8.7–21.2	5.9–18.4
Left atrium size/aorta diameter	8.7–11.3	1.4–18.5

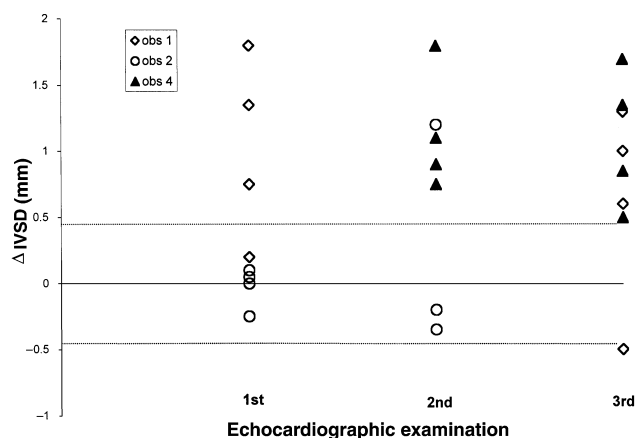


Fig. 1. Difference (expressed in mm), between each observer and the referential observer (observer 3), of mean measurements of IVSD performed in four cats on three different days. The dotted lines represent the standard deviation of within-day variability for observer 3. Switchability (i.e. ability of any observer to replace observer 3 for all cats involved) would have been acceptable if differences for a given observer lay between the dotted lines.

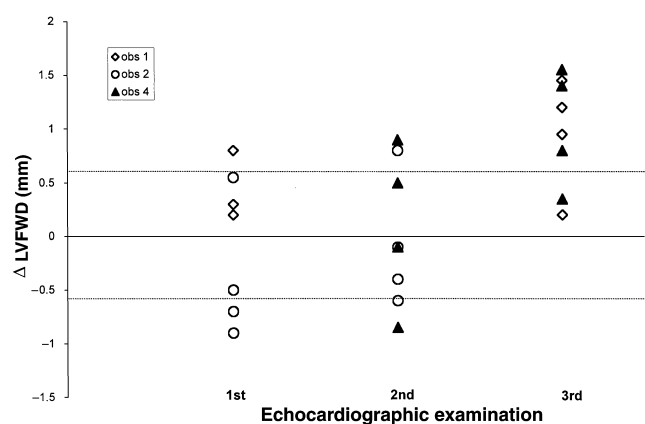


Fig. 2. Difference (expressed in mm), between each observer and the referential observer (observer 3), in mean measurements of LVFW performed in four cats on three different days. The dotted lines represent the standard deviation of within-day variability for observer 3. Switchability (i.e. ability of any observer to replace observer 3 for all cats involved) would have been acceptable if differences for a given observer lay between the dotted lines.

was performed as in a clinical situation (i.e. near the consulting room). This method was selected because, by definition, the variability in such conditions could not be compared to that previously obtained in anaesthetized cats (Moise et al., 1986b) or in animals accustomed to the observers and trained for the procedure (Young and Scott, 1998).

The experimental design of this study has certain limitations. First, only four animals were used, but the aim of this study was to assess the inter- and intra-observer variability, and not the inter-cat variability. Secondly, it would be very unusual to have repeated echocardiographic examinations within 3 weeks on the same animal in routine practice, but such repeated examination would be realistic in clinical trials. We deliberately selected such a design because a limited period of time guaranteed that (i) any biological changes occurring in a given animal would be relatively limited, and (ii) the level of experience for a given observer would be considered constant. Thirdly, the differences between observers in this study is only applicable to the group of persons involved here, but such criticism however could be made for any study involving comparison of skills. The level of experience and the observer are moreover confounded factors, but the echograph was exactly the same and this study was blinded and randomized. Similar designs have very often been selected in previous studies (Moise et al., 1986b; Young and Scott, 1998; Pickersgill et al., 2001).

The main goal of this trial was not to document ‘biological’ variability, i.e. inter-cat variability, but to obtain numerous data from several different investigators on the same subjects, in order to determine inter- and intra-observer variability. The total number of examinations was 96, and no similar study involving four observers and so many repeated measurements per animal has been published in cats. In one previous study (Moise et al., 1986b), a single observer recorded M-mode echocardiograms ( $n = 50$ ) in 10 healthy cats anaesthetized with a combination of ketamine and acepromazine, once weekly for 5 weeks. Day-to-day variability and within-day intra-observer variability were also documented in seven horses that were perfectly accustomed to the echocardiographic procedures (Young and Scott, 1998), but only one measurement was performed by a single observer on each horse, once a day at the same time, on six consecutive days ( $n = 42$ ). Moreover, the measurements were not blinded. Thus, these two studies documented the variability solely for one observer.

The mean values of repeated measurements in the three healthy cats by the four observers were similar to those

previously described in non-anaesthetized cats (Jacobs and Knight, 1985; Moise et al., 1986a). The mean duration of the echocardiographic measurements was similar to that obtained in another study (Snyder et al., 2001) for observers 2 and 3, but was longer for the other two.

No data are available for within-day intra-observer variability of the echocardiographic examination in awake cats. The CVs for all measurements performed by observer 3 were between 6 and 12%, except for LFWD (13%), RVDD (33%) and IVSS (15%). Between-day intra-observer variability has already been documented in cats (Moise et al., 1986b). The mean inter-day CVs in echographic measurements performed in anaesthetized healthy cats by a single observer were 6, 9, 9, 9 and 10% for IVSS, LVFWS, IVSD, LVFWD and LVSD, respectively. These results are close to those observed for observer 3 in the present study (16, 7, 12, 11 and 15%, respectively), even if generally lower. This difference may be because the animals in the present study were awake. Even if the animals did not struggle or resist, they were perfectly immobile as under anaesthetized conditions. However, our results demonstrate good within-day and between-day intra-observer variability of echocardiographic examination in awake cats when a trained observer is used, except for RVDD for which the highest CV values (30–40% in average) were observed. The high variability in this measurement can probably be explained by the relative difficulty in performing echocardiographic examination of the right ventricle. Other authors have suggested that this problem may result from the irregular shape, highly trabeculated contours and anatomic position of the right ventricle (Fox et al., 1985). In other studies, overall CV values (dependent on numerous factors, or at least on observers, cats, days, and ultrasonographic system) were 19 (Moise et al., 1986a), 25 (Jacobs and Knight, 1985), 37 (Sisson et al., 1991) and 47% (Fox et al., 1985). Data in the present study confirm these findings and indicate that RVDD may be of limited clinical value in follow-up studies, because of its poor within-day and between-day intra-observer variability.

The selection of critical end-points for any trial involving repeated measurements must, to ensure a meaningful clinical interpretation, take into account the variability of the measurements. The SD values of the reference observer (for both within-day and between-day intra-observer variability) obtained for the ventricular measurements (except RVDD), SF and LA/Ao were 0.5–1.3 mm, 6%, and 0.06–0.08, respectively. This suggests that care should be taken when interpreting repeated measurements with lower SD amplitudes than these values. For example, a decrease of 0.5 mm in IVSD or 1 mm in IVSS, as found by the reference observer in a clinical trial, should not be interpreted to imply clinical improvement.

The other aims of this study were to evaluate the effect of experience of the observer on the within-day and between-day intra-observer variability of echocardiographic measurements, and also to determine whether the most experienced observer could be replaced by a less-experienced observer. Our results clearly show that within-day intra-observer variability of the beginner, compared with that of other observers, was poorest for all parameters but one, and that of the most experienced observer was the best for half of the parameters. Observers 1 and 2, who had less experience but were well trained, generally gave intermediate results. Between-day intra-observer variability was better than within-day variability for most measurements in the case of the beginner, and was also better than the

between-day variability of the other more experienced observers for certain parameters. This result indicates that, for the beginner, the difference in mean measurements between days was at most equal to the differences between consecutive measurements within a day. This better between-day variability may be explained by the fact that, for any observer with good within-day variability (i.e. with a low within-day SD value), any small between-day variation may induce an increase in the SD, which may be greater than that of an observer with a poor within-day intra-observer variability. In addition, an interaction between the cat and observer was observed for IVSD, LVDD and LVFWD, which means that any of the observers (compared with the others) might over- or underestimate a given parameter depending on the cat under evaluation. This interaction indicates that the variability observed in the present study is less than the variability, which would be observed with a larger number of cats.

Our results clearly show that observer 3 could not be replaced by any of the other observers in a follow-up echocardiographic examination, and that the other observers usually overestimated the values obtained by the reference observer. One consequence is that, for a similar or higher SD value, the CV value of a less experienced observer may indeed be similar to or (because of the higher mean value of the measurement) even lower than that of the reference observer. For example, if the mean  $\pm$  SD values for a given parameter are  $4 \pm 0.6$  and  $6 \pm 0.9$  mm for the reference observer and another observer, respectively, the corresponding CV values will be 15% for both of them. In other words, if further studies confirm this tendency for less experienced observers to overestimate, then it would be better to express within-day and between-day intra-observer variability in terms of SD, and not CV, especially for comparisons between observers.

In conclusion, our results are, as in validations of any technique, only relevant to our conditions (site, observers, cats and materials). We nevertheless believe that the variability in ultrasonographic assessments needs to be taken into consideration and documented in any article involving echocardiographic procedures. The CV or SD values, and the number of observers and their level of experience, should be given to avoid misinterpretation of the data presented.

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