

## Innocent Cardiac Murmur in Puppies: Prevalence, Correlation with Hematocrit, and Auscultation Characteristics

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**Background:** The aims of this study were to establish the prevalence of innocent cardiac murmurs in clinically healthy puppies, to investigate a possible correlation between the presence of an innocent murmur and hematocrit, and to describe the auscultation characteristics of innocent murmurs.

**Hypothesis:** Lower hematocrit contributes to the genesis of innocent murmurs.

**Animals:** Five hundred and eighty-four client-owned clinically healthy puppies, between 20 and 108 days old.

**Methods:** Two cross-sectional surveys with a 1-year ( $n = 389$  pups) pilot and a half-year ( $n = 195$  pups) principal study periods. Cardiac auscultation was performed by a single, board-certified cardiologist. Hematocrit was measured with an automatized hematology analyzer. Echocardiography was performed only on puppies with a cardiac murmur in the principal study.

**Results:** In the pilot study, 15% of the dogs had a murmur. Innocent murmur was diagnosed in 28% of the 195 dogs in the principal study. Innocent murmurs were systolic, mostly with a musical character and with a maximal intensity of 2 of 6, and mostly with the point of maximal intensity in the left cardiac base. The hematocrit was significantly lower in the group with a murmur compared to the group without ( $P = .023$ ).

**Conclusions and Clinical Importance:** Innocent murmur was a common finding in puppies at the age when the first veterinary controls usually take place. Physiologic anemia contributes to the genesis of innocent murmurs in puppies. Rising hematocrit in growing puppies can explain the spontaneous disappearance of innocent murmurs with aging. Hematocrit did not differentiate innocent murmurs from abnormal murmurs.

**Key words:** Anemia; Congenital; Dogs; Physiologic; Screening.

Cardiac auscultation is routinely performed on each pup on the first and subsequent veterinary health checks, to detect murmurs.<sup>1,2</sup> Although a cardiac murmur may be indicative of a congenital cardiac anomaly, a murmur may be present with no underlying heart disease, usually called an innocent murmur.<sup>1–10</sup> Deciding whether a murmur is innocent or the result of a cardiac anomaly could be challenging for general practitioners, as the diagnosis is based solely on auscultation.<sup>11–15</sup> This decision, however, is important, because a pup with a presumably pathologic murmur should ideally be referred to a veterinary cardiologist.<sup>1,2</sup>

Although physiologic anemia has been described to contribute to the development of innocent murmurs in children,<sup>8,16</sup> to our knowledge there are no studies that have investigated this in puppies. Also, we have found no information concerning the prevalence of cardiac murmurs in clinically healthy puppies at the age group when the first veterinary health checks usually take place.<sup>17</sup> The present study, thus, aims to answer the

### Abbreviations:

CI	confidence interval
SD	standard deviation
MANOVA	multivariate analysis

following questions. What is the prevalence of innocent murmurs in clinically healthy puppies at 2–3 months of age? Is there a correlation between the presence of an innocent cardiac murmur and a lower hematocrit?

## Materials and Methods

### Sub-Studies

The study was a cross-sectional survey with 2 separate parts. The first part, called the *pilot study*, was conducted over 12 months, from February 2013 until February 2014. The second part, called the *principal study*, was conducted over 6 months, from July 2014 until January 2015. The only difference between the pilot and the principal study was that in the principal study an echocardiogram was performed on dogs that had a cardiac murmur.

The pilot study had 2 research questions, namely identifying the prevalence of cardiac murmurs in clinically healthy puppies at the age when the first veterinary consults usually take place, and testing for a correlation between hematocrit and the presence of cardiac murmurs. The principal study applied the same questions to innocent cardiac murmurs.

### Animals

All dogs were client-owned clinically healthy puppies. Breeders of the dogs of the pilot and the principal studies participated in a voluntary screening program for congenital porto-systemic shunts. Breeders of dogs of predisposed breeds brought their litters and imported individual puppies to the clinic for individual measurement of fasted blood ammonia concentration. In the pilot study

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389 puppies were enrolled and none were excluded. Eleven breeds were represented: 295 Cairn terriers (76%), 16 Yorkshire terriers, 15 Irish wolfhounds, 13 Norfolk terriers, 13 Bernese mountain dogs, 10 Stabyhouns, 9 West Highland white terriers, 5 pugs, 5 Scottish terriers, 4 Norwich terriers, and 4 Jack Russell terriers. The age of the dogs varied from 20 to 108 (mean 53) days; the youngest Cairn terrier was 47 days old, and the oldest was 80 days old.

In the principal study 210 puppies were enrolled. All, but 1 puppy, were part of the shunt-screening project. The remaining 1 puppy was referred to the cardiology service for evaluation of a cardiac murmur. This boerboel pup was added to the hematocrit-innocent murmur correlation analysis because it had an innocent murmur and the hematocrit value was available. Of the 210 puppies 15 were excluded from the hematocrit-innocent murmur correlation analysis. Fourteen of these (7 Irish wolfhounds, 4 white German shepherd dogs, and 3 Bernese mountain dogs), actually all the large-breed puppies (except for the boerboel), were excluded because tachypnea-induced increased respiratory sounds prevented the investigator from recognizing soft cardiac murmurs. One Cairn terrier was excluded from the hematocrit-innocent murmur correlation analysis because it had a congenital cardiac anomaly. After exclusions, 195 puppies remained for further analyses, representing 7 breeds: 147 Cairn terriers (75%), 18 Jack Russell terriers, 14 Yorkshire terriers, 8 Norfolk terriers, 4 Scottish terriers, 3 pugs, and 1 boerboel. The age of the puppies varied from 45 to 92 (mean 54; median 53) days.

### **Blood Test**

To measure blood ammonia concentration, approximately 2 mL of venous blood was taken via jugular venipuncture by a single experienced veterinary technician (HvE). The sample was sent immediately to the laboratory in a vacutainer tube containing EDTA as anticoagulant. The surplus blood sample was used to measure the hematocrit using an automatic hematology analyzer system<sup>a</sup> within 60–120 minutes. The hematocrit was measured only after all the puppies of that specific day had been auscultated, so that the investigator would not be biased.

### **Auscultation**

The breeders gave oral permission to the single investigator (VSz, ECVIM board-certified cardiologist) to perform the cardiac auscultation, whereas they were waiting for the blood ammonia results. Each dog was identified by the chip number. The dogs were placed one by one on the examination table in a quiet examination room and were examined in standing position using a pediatric nonelectronic stethoscope. The membranous side of the stethoscope with a diameter of 30 mm was used. The regions of the heart base and apex were auscultated on the left and right hemithorax. The left side was auscultated first, then the right, and finally the left side again. If a murmur was detected, the following parameters were noted: point of maximal intensity (left or right hemithorax, apex or base), intensity (scale 1–6, 6 being the loudest), place in the cardiac cycle (systolic and/or diastolic or continuous), and additional characteristics, such as musical character and beat-to-beat variability in murmur intensity (ie, intermittently audible murmur).<sup>4,18</sup> A murmur was defined as intermittent if a soft (1 or 2 out of 6) murmur was heard for the first time on the left hemithorax, but disappeared while the auscultation was still performed on the same location and could not be identified when the left hemithorax was auscultated again. Auscultation of a pup lasted approximately 1 minute. Heart rates were not recorded.

Each dog was classified based on the auscultation into one of the following 4 categories: no murmur, suspected congenital

cardiac anomaly, suspected innocent murmur, and inability to judge the presence of a murmur. Dogs in the last category were excluded from further analysis. A murmur was suspected to be innocent, if it was audible intermittently or with every heart beat and had the reported characteristics of an innocent murmur: early systolic with an intensity of 1 or 2 of 6 and a musical character with the point of maximal intensity in the region of the left cardiac base.<sup>4</sup>

### **Echocardiography**

Between the pilot and the principal study periods, a single Cairn terrier pup with a moderately loud (3 of 6) systolic musical murmur and 4 Cairn terrier pups (all from the same 50-day-old litter) with an intermittent systolic murmur were examined with an echocardiogram. The point of maximal intensity of the murmur in all the 5 puppies was in the region of the left cardiac base. The maximal murmur intensity in the latter 4 puppies was 1 of 6. In the principal study each dog with a cardiac murmur underwent a focused echocardiogram ( $n = 30$ ), except for the puppies with an intermittent murmur.

The focused echocardiograms<sup>b</sup> were performed, by the same cardiologist who did the cardiac auscultation, immediately after cardiac auscultation when the hematocrit results were not yet available. As the auscultation and the focused echocardiogram were performed by the same person, this part of the investigation was not blind. The puppies were examined in right lateral recumbency without sedation with manual restraint. Standard 2-dimensional right parasternal long axis views with color Doppler mode were used to look for mitral, aortic, and relevant tricuspid valve regurgitation, atrial, and ventricular septal defects. Right parasternal short axis images were used to measure the peak blood flow velocity in the pulmonic artery with continuous wave Doppler technique to rule out pulmonic stenosis. With color Doppler mode, the same image was used to look for a patent ductus arteriosus, atrial, and ventricular septal defects and relevant tricuspid valve regurgitation. A subcostal view was used to measure the peak blood flow velocity in the aorta using continuous wave Doppler mode to rule out aortic stenosis.<sup>5</sup> Blood flow velocities in the pulmonic artery and in the aorta below 2.0 m/s were considered to be physiologic, whereas a blood flow velocity above 2.0 m/s would be considered to be the cause of a murmur.

### **Statistics**

A commercially available software package<sup>c</sup> was used for data analysis. Because Cairn terriers outnumbered the other breeds, the findings on the Cairn terriers and those on all the other breeds were analyzed separately in a subanalysis. Normality of data was assessed with the Kolmogorov–Smirnov test. A possible correlation between the presence of a cardiac murmur and the hematocrit was tested with Student's *t*-test. Multivariate analysis (MANOVA) was performed to investigate whether the hematocrit or the age of the dogs correlated with the presence of (innocent) murmur, after having performed Levene's test of equality of error of variances. The *P* values of  $<.05$  were considered to be significant. Results were described as mean (range) if the data were normally distributed. The possible correlation between the hematocrit and age of the dogs were investigated with the Pearson correlation test.

## **Results**

### **Murmur**

In the pilot study, 58 of the 389 clinically healthy puppies had a cardiac murmur (15%). The murmur had a musical character in 43 of the 59 cases (73%). The

murmur was present only intermittently in 5 dogs (8%). The intensity of the murmur was 1 of 6 in 22 dogs (37%) and 2 of 6 in 31 dogs (53%).

In the principal study, 54 of the 195 clinically healthy puppies had a cardiac murmur (prevalence of 28%). This includes the 1 Cairn terrier where a congenital cardiac anomaly was suspected based on auscultation, which dog was subsequently excluded from the hematocrit–murmur correlation analysis, but it does not include the boerboel with an innocent murmur that was added only for the hematocrit–murmur correlation analysis. The innocent murmurs had a musical character in 49 of the 54 puppies (91%). The intensity of the innocent murmur was 1 of 6 in 10 dogs (19%) and 2 of 6 in 20 dogs (37%). The murmur was only intermittently present in 24 dogs (44%), in each case with a maximal intensity of 1 of 6. The point of maximal intensity of the innocent murmurs was localized on the left hemithorax (generally in the basal region) in all but 2 dogs. In these 2 puppies the murmur was best heard in the region of the right cardiac base; one intermittently and the other one with an intensity of 2 of 6. The Cairn terrier with a suspected congenital cardiac anomaly had a systolic nonmusical murmur with a stenotic character, with the point of maximal intensity in the region of the left cardiac base and an intensity of 3 of 6.

Though the heart rate was not recorded, it did not typically change remarkably during the auscultation of the individual dogs.

### *Echocardiography*

The Cairn terrier that was examined outside the pilot and principal study periods was 65 days old and had a systolic murmur with the point of maximal intensity at the region of the left cardiac base and an intensity of 3 of 6. Echocardiography showed a mildly increased peak systolic velocity in the aorta of 2.8 m/s with no other abnormalities on the heart.

Echocardiography of the 4 Cairn terriers with intermittent systolic cardiac murmurs of a maximal audible murmur intensity of 1 of 6 revealed no abnormalities; the mean peak systolic blood flow velocities in the aorta and pulmonary artery were respectively 1.5 m/s (range 1.2–1.9 m/s) and 0.87 m/s (range 0.71–1.1 m/s).

In the principal study, 31 puppies underwent a focused echocardiogram. The Cairn terrier that was suspected to have a congenital cardiac anomaly based on auscultation turned out to have a double-chambered right ventricle with a maximum calculated pressure gradient of 55 mmHg. On 29 of the remaining 30 puppies, no abnormalities were found on echocardiogram. In 1 pup, however, a mild mitral valve regurgitation was found on color Doppler images with no other cardiac changes. The mean peak systolic aortic flow velocity in the 30 dogs was 1.35 m/s (range 1.05–1.87 m/s) and the mean peak pulmonic arterial velocity was 0.99 m/s (range 0.74–1.26 m/s). With color Doppler imaging, mild (physiologic) pulmonic valve regurgitations were found in 12 of the 30 puppies and mild (physiologic)

tricuspid valve regurgitations in a further 6.<sup>19,20</sup> Echocardiogram showed no abnormalities in the 69-day-old boerboel.

### *Hematocrit*

In the pilot study, the mean hematocrit of the 389 pups was 32.0% (SD 3.1%, range 24.6–46.7%). The mean hematocrit of the group without a murmur (32.2%, SD 3.1; n = 330) was significantly ( $P = .003$ ) higher than the mean hematocrit of the group with a murmur (30.9%, SD 2.8; n = 59). The mean age of the group without a murmur (52.9 days, SD 7.7; n = 330) was not significantly different ( $P = .2$ ) from the mean age of the group with a murmur (51.6 days, SD 6.2; n = 59).

The possible effect of breed was investigated. When the group of Cairn terriers with a murmur (n = 53) was compared to the group of Cairn terriers without a murmur (n = 242), the same results were found as for the total group. Cairn terriers without a murmur had a mean hematocrit of 32.2% (SD 2.5%), which was significantly ( $P = .001$ ) higher than the mean hematocrit of the group of Cairn terriers with a murmur, 30.9% (SD 2.5%). The mean age of Cairn terriers without a murmur (53.1 days, SD 6.3) was not significantly different ( $P = .47$ ) from the mean age of the Cairn terriers with a murmur (52.4 days, SD 4.6).

However, when the mean hematocrit value of the group consisting of all non-Cairn terrier breeds (n = 94) was looked at, no statistically significant difference ( $P = .61$ ) was found between the subgroup with a murmur (mean hematocrit 31.3%, SD 4.9; n = 6) and the subgroup with no murmur (mean hematocrit 32.2%, SD 4.4; n = 88). The mean age of the pups with and without a murmur also did not significantly differ in the non-Cairn terrier group ( $P = .07$ ).

In the principal study group, the mean hematocrit of the 195 pups was 30.5% (SD 3.3%, range 23.2–40.8%). The mean hematocrit of the group without a murmur (30.8%, SD 3.4; n = 141) was significantly ( $P = .023$ ) higher than the mean hematocrit of the group with a murmur (29.6%, SD 2.7; n = 54). The mean age of the group without a murmur (53.9 days, SD 7.8; n = 141) was not significantly different ( $P = .8$ ) from the mean age of the group with a murmur (53.6 days, SD 7.6; n = 54).

When the group of Cairn terriers with a murmur (n = 45) was compared to the group of Cairn terriers without a murmur (n = 102), the same results were found as for the total group. The mean hematocrit in Cairn terriers without a murmur (30.8%, SD 3.1) was significantly ( $P = .005$ ) higher than the mean hematocrit of the group of Cairn terriers with a murmur (29.3%, SD 2.5). The mean age of Cairn terriers without a murmur (n = 102) was 53.5 days (SD 7.2 days), which was not significantly different ( $P = .49$ ) from the mean age of the Cairn terriers with a murmur (n = 45), which was 52.7 days (SD 4.8 days).

When the mean hematocrit value of the group that consisted of all non-Cairn terrier breeds (n = 48) was

considered, no statistically significant difference ( $P = .77$ ) was found between the subgroup with a murmur (31.3%, SD 3.0;  $n = 9$ ) and the subgroup with no murmur (30.9%, SD 4.3;  $n = 39$ ). The mean age of the pups with a murmur (57.7 days, SD 15.2;  $n = 9$ ) and those without (54.7 days, SD 9.2;  $n = 39$ ) did not significantly differ in the non-Cairn terrier group either ( $P = .447$ ).

The MANOVA showed both in the pilot and the principal study that the presence of a murmur was correlated with the hematocrit ( $P = .003$  and  $.023$ , respectively), but not to the age of the dogs ( $P = .211$  and  $.807$ , respectively).

A comparable, weak, but significant correlation ( $R = 0.339$  and  $0.355$ ;  $P < .001$ ) was found between the hematocrit and the age of the dogs in both the pilot (hematocrit =  $0.247 + 0.001$  [age in days]) and the principal (hematocrit =  $0.224 + 0.002$  [age in days]) study.

The Cairn terrier puppy that was examined outside the 2 study periods with a mildly increased aortic flow velocity had a hematocrit of 37.0%.

## Discussion

In our pilot study, 15% of 389 puppies, with the mean age of 7.5 weeks (53 days) had an audible murmur which was thought, but not proven, to be innocent.<sup>4</sup> In the principal study 28% of the 195 puppies with the mean age of 54 days had an innocent cardiac murmur.

In all puppies of the pilot study, the murmur was thought to be innocent based on earlier descriptions in the dog and human.<sup>4-10</sup> The major limitation of the pilot study is that no echocardiogram was performed on puppies with a murmur. Neither were the dogs later rechecked for spontaneous disappearance of the murmur. Although a free of charge recheck examination of all the puppies with a murmur was offered to the breeders, only a couple of puppies returned.

Cairn terriers have not been reported to be predisposed to congenital aortic or pulmonic stenosis,<sup>14</sup> but we identified a Cairn terrier pup with a mild aortic stenosis and a musical type of murmur. This murmur was louder than 2 of 6 (2 of 6 was the loudest innocent murmur in our principal study results). A limitation of the principal study is that dogs with an intermittently audible murmur did not undergo an echocardiogram. We thought that the auscultation and echocardiographic results of the 4 dogs with intermittently audible innocent murmurs examined between the 2 study periods could be safely extrapolated to the 24 puppies with the intermittently present soft murmur of the principal study.

It is difficult to compare the prevalence of innocent murmurs in our study to published studies, because major differences in the populations may affect findings. Innocent murmurs have been found in 58% of 105 clinically healthy adult whippets and in 6-12% of 95 adult dogs of different breeds.<sup>5,17</sup> Athletic breeds (such as whippet) are more prone to have innocent murmurs because of larger cardiac output.<sup>5</sup> In children, the prevalence of innocent murmurs is 50-90%.<sup>6,10,12</sup>

The prevalence of murmurs, especially the intermittent ones, was significantly higher in the principal study ( $P = .007$ ). The most likely explanation for this finding is the investigator's gain in experience in recognizing quickly very soft and intermittently audible murmurs.

The mean hematocrit of puppies at the mean age of 7.5 weeks was 30.5 (pilot) or 32.0% (principal study), which is lower than the reference values of adult dogs. This is consistent with physiologic anemia, which is known to be present in young animals and children.<sup>8,21</sup> For example, a longitudinal study of 34 Beagles and 44 Labrador retrievers found at the age of 3.1-8 weeks a median hematocrit of 36% (29-41%) in the Beagles and a median hematocrit of 32% (20-38%) in the Labrador retrievers.<sup>21</sup> In the same dogs between 8.1 and 16 weeks of age, median hematocrit had risen to 38% (28-46%) for the Beagles and 37% (20-69%) for the Labrador retrievers.<sup>21</sup> Increasing hematocrit in growing puppies could explain why innocent murmurs tend to disappear spontaneously with aging.

In both parts of our study, puppies with cardiac murmurs had significantly lower hematocrit values than puppies with no murmur; both substudies had a low  $P$ -value. Cardiac murmurs are known to be caused by turbulent blood flow.<sup>8,22,23</sup> The chance of turbulent blood flow increases with the lower blood viscosity that results from lower hematocrit.<sup>8</sup> This relationship is described by the Reynolds number.<sup>8,24</sup> In addition to lower blood viscosity, a higher cardiac output has also been suggested to contribute to the presence of innocent murmurs.<sup>8,25-27</sup> Although the present study has not aimed to investigate the cardiac output, higher cardiac output may be present in individuals with lower hematocrit, as anemia has been shown to result in a hyperdynamic circulation.<sup>28</sup> Blood flow velocities measured in the aorta and pulmonic artery in the puppies with an innocent murmur were comparable to the reported reference values of healthy dogs.<sup>20,29</sup>

The reason why no correlation was found between a lower hematocrit and murmurs in the non-Cairn terrier puppies is difficult to explain. One reason could be that the number of non-Cairn terrier dogs was quite low compared to the Cairn terrier group and thereby the power to detect a difference was too low. Another explanation could be that the non-Cairn terrier group in the pilot study included many large-breed dogs. A thicker thoracic wall may be speculated to dampen a soft murmur to an inaudible level. Another difficulty may arise from the fact that large-breed dogs are more likely to pant or to have tachypnea. The increased respiratory sounds caused by tachypnea might have prevented the examiner from picking up soft innocent cardiac murmurs. For this reason, large-breed dogs with tachypnea or panting were excluded from further analysis in the principal study, but the results of the remaining small-breed dogs turned out to be the same, ie, no correlation between hematocrit and innocent cardiac murmurs.

Because there is considerable overlap between the hematocrit values of the group with murmur and that without, measuring hematocrit would not help to differentiate an innocent murmur from a pathologic one in an individual puppy. Moreover, the difference in

hematocrit between the 2 groups is very small. This small difference, however, seems to be large enough to create a soft murmur. Excitement may also contribute to the audibility of (intermittent) murmurs.<sup>30</sup>

We conclude that physiologic anemia contributes to the genesis of innocent cardiac murmurs in puppies. Physiologic murmur can be expected in 15–25% in clinically healthy puppies brought for the first veterinary control. A murmur is likely to be innocent if it is: soft (with a maximal intensity of 2 of 6), systolic, has a musical character and the point of maximal intensity is located in the region of the left cardiac base.

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### Footnotes

<sup>a</sup> Advia 2120i, Siemens Healthcare Diagnostics GmbH, Eschborn, Germany.

<sup>b</sup> Philips HD 11 XE ultrasound machine equipped with an 8–3 MHz phased array transducer, Bothell, WA, USA.

<sup>c</sup> IBM Statistics SPSS 21.0, IBM Corp., Chicago, IL, USA.

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*Off-label Antimicrobial Declaration:* Authors declare no off-label use of antimicrobials.

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