(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 December 2014 (18.12.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/198753 A1

(51) International Patent Classification:
A61B 6/00 (2006.01)

(21) International Application Number:
PCT/EP2014/062097

(22) International Filing Date:
11 June 2014 (11.06.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
13171434.7 11 June 2013 (11.06.2013) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

[Continued on next page]

(54) Title: A COMPUTER IMPLEMENTED METHOD FOR MEASURING SPECIFIC HEART CHAMBERS FROM HEART RADIOGRAPHIC IMAGES AND COMPUTER PROGRAM PRODUCTS THEREOF.

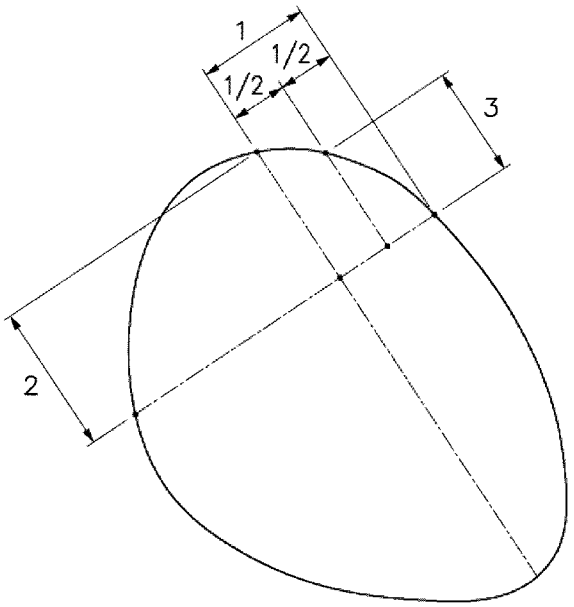


Fig. 1

(57) Abstract: A computer implemented method for determining enlargement of specific heart chambers from heart radiographic measurements and computer program products thereof The computer implemented method is based on radiographic measurements of heart size performed on thoracic radiographs images using as a reference the long L and short S cardiac axes of the heart and on a comparison between some of the measurements obtained on thoracic radiographs of healthy subjects or subjects with degenerative mitral valve disease (DMDV). The method proposes the following three radiographic measurements: R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit; top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and LA roof equal to the distance from midpoint of R-half-VHS to LA roof.15.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

A computer implemented method for measuring specific heart chambers from heart radiographic images and computer program products thereof

Field of the invention

The present invention generally refers to imaging methods. Particularly, present invention refers to a computer implemented method for measuring specific heart chambers based on specific measurements imposed on thoracic radiographs images and computer program products thereof.

Although tests using heart radiographic images measurements according to the invention have been conducted with dogs it is considered the application of the measures are extensible to other mammals including humans as evidenced with some publications that will be following referred.

The imaging measurements achieved by this invention provide data that are suitable for establishing a diagnosis of left atrial enlargement (LAE).

Background of the invention

The vertebral heart scale (VHS) method is an established indicator of global heart enlargement in dogs but is relatively nonspecific for enlargement of individual heart chambers.

In (Flavio R. Alves et al, 2012) [1] related to anatomical and radiographic appearance of the capuchin monkey thoracic cavity, it was declared that "the radiographic evaluation allowed the description of biometric values associated with the cardiac silhouette and thoracic structures. Application of the VHS (vertebral heart size) method showed positive correlation ($p<0.05$) with depth of the thoracic cavity, as well as between the body length of vertebrae T3, T4, T5 and T6 and the cardiac length and width." From this paragraph it can be inferred the possible usefulness of the VHS in capuchin monkey that can sustain as hypothesis its utility also in humans.

Radiographic left atrial bisecting line (LABL) is defined as a line arising at a 45-degree angle from the intersection of VHS long (L) and short (S) axis of the heart and extending to the border of the left atrium (LA) (Sánchez et al, 2010) [5].

A recent study comparing VHS and radiographic left atrial bisecting line (LABL) measurements to each other and to left atrial to aortic root ratio (LA/Ao) found that LABL was not significantly different in dogs with and without congestive heart failure (CHF) as opposed to VHS measured on the left lateral view (Hernández-López et al, 2012) [6]. Researchers of the original study (Sánchez et al, 2010) [5] argued that the lack of correlation between LABL and LA/Ao measurements was due to difficulty in accurately

estimating the limit of the left atrium (LA) as it is obscured by normal anatomical structures and by perihilar pulmonary edema in the setting of CHF.

The aim of this invention is to evaluate the usefulness of new radiographic measurements mainly to detect left atrial enlargement (LAE) overcoming the above difficulties.

With the help of a few simple measurements imposed on thoracic radiographs images, information can be collected determining size of individual heart chambers.. These new radiographic image measurements which differ from previous image measurements used as indicator of global heart enlargements are data useful for establishing a diagnosis of left atrial enlargement (LAE).

Summary of the invention

New measurements were obtained as the distance from the intersection of the long (L) and short (S) axis of the heart to caudal heart limit (R-half-VHS), the distance from the intersection of the L and S axis of the heart to ventral border of carina (top-half-VHS), the sum of these measurements (Sum R-Top) and the distance from midpoint of R-half-VHS to LA roof (LA roof measurement).

LABL was defined as a line arising at a 45-degree angle from the intersection of L and S axis of the heart and extending to the border of the left atrium and VHS was measured as described previously (Buchanan, 2000) [7]. LA/Ao ratio was obtained by two-dimensional ultrasonographic mode from right parasternal short axis view at the level of the aortic valves in early diastole.

The provided computer implemented method for measuring specific heart chambers from heart radiographic measurements images, according to the invention comprises the known steps of:

a) obtaining, through a detector, thoracic radiographs images of a subject;

b) performing, a processor running in a computing device, on said thoracic radiographs images, measurements using as a reference the long L and short S cardiac axes;

c) comparing, said processor, some of these radiographic images measurements with equivalent radiographic images measurements of healthy subjects and of subjects with degenerative mitral valve disease (DMVD);

d) analysing, the processor, similarities and differences between the compared measurements, and

e) storing the results in an storage medium such as a database or a memory.

According to this invention at least three of the cited new measurements are performed on the thoracic radiographs images:

R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart border;

Top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

LA roof equal to the distance from midpoint of R-half-VHS to LA roof.

Besides a further fourth measurement is used, termed Sum R-Top equal to the sum of R-half-VHS and top-half-VHS.

Sum R-Top, LA Roof measurement and LABL showed high sensitivity (all of them 84.6%) and specificity (90.5%, 95.2 % and 95.2 % respectively). For instance, these obtained results could be used to detect Left Atrial Enlargement (LAE). Maximal reference values were 3.1v, 1.2v and 1.8v respectively. Good significant correlation between these measurements and LA/Ao was found. LA Roof measurements and Sum R-Top appear to be interesting alternatives to LABL in detecting LAE in dogs with degenerative mitral valve disease (DMVD).

These new measurements were compared to VHS, LABL and left atrium to aortic root ratio (LA/Ao) in healthy dogs and dogs with (DMVD). Healthy patients (n=10) and dogs with DMVD (n=24) were prospectively selected to be included in a study.

The subject matter described herein can be implemented in software in combination with hardware and/or firmware, or a suitable combination of them. For example, the subject matter described herein can be implemented in software executed by a processor.

Brief description of the drawings

In the attached Fig. 1 the new four proposed measurements are depictured on a radiographic image, taken by a radiography imaging system or X-ray apparatus (not shown), of a heart of a dog.

The heart is schematically depicted by a contour line and the following references have been indicated in the Fig.1:

1: R-Half VHS

2: Top Half VHS

3: LA Roof

Description of the invention

Statistical AnalysisA multivariate regression model considering ACVIM (American College of Veterinary Internal Medicine) class (clinical stage of DMVD) as quantitative

response variable was analysed using all potential diagnostic markers as explanatory variables.

Interactions between markers and quadratic terms were also evaluated. Non-significant terms were removed from the model.

All statistical decisions were based on a 5% significance level. Statistical Analysis was performed using SAS System v9.2 (SAS Institute Inc., Cary, USA).

Statistical combination of these new measurements:

By statistical combination of measurements R-half-VHS, VHS, top-half-VHS, LA roof measurement, LABL and Sum R-Top, a new tool was obtained as follows:

After making a selection of variables and compare interactions and quadratic terms, a predictive model based on joint optimization of the tools above is as follows:

$$PRED = -3.8164 + Top_Half_VHS * 2.7707 + LA_Roof * 2.3931 + Top_Half_VHS*LA_Roof * -1.0379$$

The "Type III Tests of Fixed Effects" table contains hypothesis tests for the significance of each of the fixed effects

Type 3 Tests of Fixed Effects

Effect	Numb DF	Den DF	F Value	Pr > F
Top_Half_VHS	1	33	8.82	0.0055
LA_Roof	1	33	13.27	0.0009
Top_Half_VHS*LA_Roof	1	33	5.50	0.0252

where:

DF: degree of freedom
F value: significance
Pr: probability

Statistical summary of the combination of these new measurements for each ACVIM class are detailed in the following Table.

	Predicted			
	ACVIM Class			
	0	B	C	D
Mean	0.30	1.31	1.91	2.25
Std	0.39	0.35	0.59	0.32

Min	-0.38	0.73	0.54	1.79
Max	0.85	1.75	2.55	2.66
N	10	7	15	5

ACVIM class: clinical stage of DMVD

Stage 0: healthy dogs

Stage B: left atrial enlargement without congestive heart failure dogs

Stage C: left atrial enlargement with congestive heart failure dogs

Stage D: left atrial enlargement with congestive heart failure refractory to treatment dogs

Results show that using the predictive formula by using Top Half VHS and LA roof measurements allows predicting the clinical stage of DMVD in dogs.

Comparisons between individual tests and composite were performed using a linear model and evaluating type I sum of squares.

Each of these sub-tables shows the net contribution of each variable (first line) and (second line) the extra contribution of the predictive formula.

Source	DF	Type I SS	Mean Square	F Value	Pr >F
R_half_VHS	1	16.00512582	16.00512582	45.76	<.0001
Pred	1	11.02083132	11.02083132	31.51	<.0001

Source	DF	Type I SS	Mean Square	F Value	Pr > F
VHS	1	13.64638711	13.64638711	39.10	<.0001
Pred	1	13.40522734	13.40522734	38.41	<.0001

Source	DF	Type I SS	Mean Square	F Value	Pr > F
Top_Half_VHS	1	21.34354351	21.34354351	61.00	<.0001
Pred	1	5.67836087	5.67836087	16.23	0.0003

Source	DF	Type I SS	Mean Square	F Value	Pr > F
LA_Roof	1	23.46758402	23.46758402	67.07	<.0001
Pred	1	3.55432036	3.55432036	10.16	0.0031

Source	DF	Type I SS	Mean Square	F Value	Pr > F
LAB	1	22.37104606	22.37104606	64.08	<.0001
Pred	1	4.67739714	4.67739714	13.40	0.0008

DF: degree of freedom

Type I SS: type I sum of squares

In all variables, the “Pred” line p-value is <0.05: this shows that the predictive formula improves separately each predictive tool. Thus, combination of new measurements Top-half and LA roof is a better tool to detect LAE.

In other embodiment, method for determining enlargement of specific heart chambers from heart radiographic measurements, comprising:

- obtaining thoracic radiographs;
- performing on said thoracic radiographs, measurements using as a reference the long L and short S cardiac axes;
- comparing some of these radiographic measurements in healthy subjects and subjects with degenerative mitral valve disease (DMVD);
- analysing similarities and differences between the compared measures, and
- storing the results.

characterized in that said size measurement on said thoracic radiographs comprise at least following three measures:

R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit;

top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

LA roof equal to the distance from midpoint of R-half-VHS to LA roof.

In other embodiment, method for determining enlargement of specific heart chambers from heart radiographic measurements, comprising:

- obtaining thoracic radiographs;
- performing on said thoracic radiographs, measurements using as a reference the long L and short S cardiac axes;
- comparing some of these radiographic measurements in healthy subjects and subjects with degenerative mitral valve disease (DMVD);
- analysing similarities and differences between the compared measures, and
- storing the results.

characterized in that said size measurement on said thoracic radiographs comprise at least following three measures:

R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit;

top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

LA roof equal to the distance from midpoint of R-half-VHS to LA roof.

wherein a fourth measure Sum R-Top equal to the sum of R-half-VHS and top-half-VHS, is further used.

In other embodiment for determining enlargement of specific heart chambers from heart radiographic measurements, comprising:

- obtaining thoracic radiographs;
- performing on said thoracic radiographs, measurements using as a reference the long L and short S cardiac axes;
- comparing some of these radiographic measurements in healthy subjects and subjects with degenerative mitral valve disease (DMVD);
- analysing similarities and differences between the compared measures, and
- storing the results.

characterized in that said size measurement on said thoracic radiographs comprise at least following three measures:

R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit;

top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

LA roof equal to the distance from midpoint of R-half-VHS to LA roof, wherein said individual heart chambers pertain to a dog and the method allowing to detect left atrial enlargement.

In other embodiment, method for determining enlargement of specific heart chambers from heart radiographic measurements, comprising:

- obtaining thoracic radiographs;
- performing on said thoracic radiographs, measurements using as a reference the long L and short S cardiac axes;
- comparing some of these radiographic measurements in healthy subjects and subjects with degenerative mitral valve disease (DMVD);
- analysing similarities and differences between the compared measures, and
- storing the results.

characterized in that said size measurement on said thoracic radiographs comprise at least following three measures:

R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit;

top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

LA roof equal to the distance from midpoint of R-half-VHS to LA roof, wherein said individual heart chambers pertain to a human being and the method allowing to detect cardiomegaly.

In other embodiment, method for determining enlargement of specific heart chambers from heart radiographic measurements, comprising:

- obtaining thoracic radiographs;
- performing on said thoracic radiographs, measurements using as a reference the long L and short S cardiac axes;
- comparing some of these radiographic measurements in healthy subjects and subjects with degenerative mitral valve disease (DMVD);
- analysing similarities and differences between the compared measures, and
- storing the results.

characterized in that said size measurement on said thoracic radiographs comprise at least following three measures:

R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit;

top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

LA roof equal to the distance from midpoint of R-half-VHS to LA roof.,

wherein said measures where compared to radiographic vertebral heart scale (VHS) measurements of healthy dogs and dogs with degenerative mitral valve disease (DMDV)

In other embodiment, method for determining enlargement of specific heart chambers from heart radiographic measurements, comprising:

- obtaining thoracic radiographs;
- performing on said thoracic radiographs, measurements using as a reference the long L and short S cardiac axes;
- comparing some of these radiographic measurements in healthy subjects and subjects with degenerative mitral valve disease (DMVD);
- analysing similarities and differences between the compared measures, and
- storing the results.

characterized in that said size measurement on said thoracic radiographs comprise at least following three measures:

R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit;

top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

LA roof equal to the distance from midpoint of R-half-VHS to LA roof.,

wherein said measures where compared to radiographic left atrial bisecting line (LABL) of healthy dogs and dogs with degenerative mitral valve disease (DMDV).

In other embodiment, method for determining enlargement of specific heart chambers from heart radiographic measurements, comprising:

- obtaining thoracic radiographs;
- performing on said thoracic radiographs, measurements using as a reference the long L and short S cardiac axes;
- comparing some of these radiographic measurements in healthy subjects and subjects with degenerative mitral valve disease (DMVD);
- analysing similarities and differences between the compared measures, and
- storing the results.

characterized in that said size measurement on said thoracic radiographs comprise at least following three measures:

R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit;

top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

LA roof equal to the distance from midpoint of R-half-VHS to LA roof.,

wherein said measures where compared to left atrium to aortic root ratio (LA/Ao) of healthy dogs and of dogs with degenerative mitral valve disease (DMDV).

In other embodiment, method for determining enlargement of specific heart chambers from heart radiographic measurements, comprising:

- obtaining thoracic radiographs;
- performing on said thoracic radiographs, measurements using as a reference the long L and short S cardiac axes;
- comparing some of these radiographic measurements in healthy subjects and subjects with degenerative mitral valve disease (DMVD);
- analysing similarities and differences between the compared measures, and
- storing the results.

characterized in that said size measurement on said thoracic radiographs comprise at least following three measures:

R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit;

top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

LA roof equal to the distance from midpoint of R-half-VHS to LA roof.

, wherein a statistical combination of measurements R-half-VHS, VHS , top-half-VHS, LA roof measurement, LABL and Sum R-Top t is performed and after making a selection of variables and compare interactions and quadratic terms, a predictive model based on joint optimization of the above measures is obtained as follows:

PRED = -3.8164 + Top_Half_VHS*2.7707 + LA_Roof * 2.3931 + Top_Half_VHS*LA_Roof * (-1.0379)

References

[1] Flavio R. Alves, Francisco B. Costa et al: Anatomical and radiographic appearance of the capuchin monkey thoracic cavity. Pesq.Vet Bras 32 (12):1345, December 2012

[2] Mai HARADA, Hiroshi KOIE et al.: Establishment of Vertebral Heart Scale in the Growth Period of the Japanese Macaque (Macaca fuscata). J. Vet. Med. Sci. 72(4): 503–505, 2010

[3] Anaemilia das N. Diniz, José R. da Silva et al: Thoracic and heart biometrics of non-anesthetized agouti (Dasyprocta primnolopha Wagler, 1831) measured on radiographic images Pesq. Vet. Bras. vol.33 no.3 Rio de Janeiro Mar. 2013

[4] X.Sanchez, D.Prandi et al: A new method of computing the vertebral heart scale by means of direct standardisation. Journal of Small Animal Practice (2012).

[5] Sánchez X., Prandi D., Domenech O. A new radiologic measurement to study left atrial enlargement in dogs with mitral insufficiency: preliminary study. ACVIM Annual Meeting, Anaheim,CA, 2010.

[6] Hernandez-Lopez J., Machen M.C., Oyama M.A. Radiographic Vertebral Heart Size and Left Atrial Bisecting Line: Interobserver variability and comparison to echocardiographic left atrial size in dogs with degenerative mitral valve disease. ACVIM Annual Meeting, Louisiana, NO, 2012.

[7] Buchanan J. Vertebral scale system to measure heart size in radiographs. Veterinary Clinics of North America Small Animal Practice, 2000; 30: 379-93.

CLAIMS

1. A computer implemented method for measuring specific heart chambers from heart radiographic images, comprising:

a) obtaining, through a detector, thoracic radiograph images of a subject;

b) performing through a processor, on said obtained subject thoracic radiograph images, measurements using as a reference the long L and short S cardiac axes;

c) comparing through said processor, some of these thoracic radiographic images measurements with thoracic radiographic images of healthy subjects and with thoracic radiographic images of subjects with degenerative mitral valve disease (DMVD);

d) analysing, through the processor, similarities and differences between the compared measures, and

e) storing the results at least in an storage medium,

characterized in that said measurements on said thoracic radiographs images comprises at least the following three measurements:

- R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit;

- top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

- LA roof equal to the distance from midpoint of R-half-VHS to LA roof.

2. Method according to claim 1, wherein a fourth measurement Sum R-Top equal to the sum of R-half-VHS and top-half-VHS, is further used.

3. Method according to claims 1 or 2, wherein said measurements where compared to radiographic vertebral heart scale (VHS) measurements of healthy dogs and dogs with degenerative mitral valve disease (DMDV).

4. Method according to claims 1 or 2, wherein said measurements where compared to radiographic left atrial bisecting line (LABL) images of healthy dogs and dogs with degenerative mitral valve disease (DMDV).

5. Method according to claims 1 or 2, wherein said measurements where compared to left atrium to aortic root ratio (LA/Ao) of healthy dogs and of dogs with degenerative mitral valve disease (DMDV).

6. Method according to claims 1 or 2, wherein a statistical combination of measurements R-half-VHS, VHS, top-half-VHS, LA roof measurement, LABL and Sum R-Top t is performed and after making a selection of variables and compare interactions and quadratic terms, a predictive model based on joint optimization of the above

measurements is obtained as follows:

PRED = -3.8164 + Top_Half_VHS*2.7707 + LA_Roof * 2.3931 + Top_Half_VHS*LA_Roof * (-1.0379)

7. A computer program product comprising computer program code means adapted to perform steps b) to e) of the method of claim 1 when said program is run on a computer, a digital signal processor, a field-programmable gate array, an application-specific integrated circuit, a micro-processor, a micro-controller, or any other form of programmable hardware.

8. A computer program product according to claim 7, further comprising program code means adapted to perform a fourth measurements Sum R-Top equal to the sum of R-half-VHS and top-half-VHS.

9. Method for determining enlargement of specific heart chambers from heart radiographic measurements, comprising:

- obtaining thoracic radiographs;
- performing on said thoracic radiographs, measurements using as a reference the long L and short S cardiac axes;
- comparing some of these radiographic measurements in healthy subjects and subjects with degenerative mitral valve disease (DMVD);
- analysing similarities and differences between the compared measurements, and
- storing the results.

characterized in that said size measurement on said thoracic radiographs comprise at least following three measurements:

R-half-VHS equal to the distance from the intersection of the L and S axis of the heart to caudal heart limit;

top-half-VHS equal to the distance from the intersection of the L and S axis of the heart to ventral border of carina; and

LA roof equal to the distance from midpoint of R-half-VHS to LA roof.

10. Method according to claim 9, wherein said individual heart chambers pertain to a dog and the method allowing to detect left atrial enlargement.

11. Method according to claim 9, wherein said individual heart chambers pertain to a human being and the method allowing to detect cardiomegaly.

12. Use of the measurements obtained according to claim 1 or 9 to detect enlargement of left atrial chamber of the heart in dogs

13. Use of the measurements obtained according to claim 1 or 9 to diagnose degenerative mitral valve disease in dogs

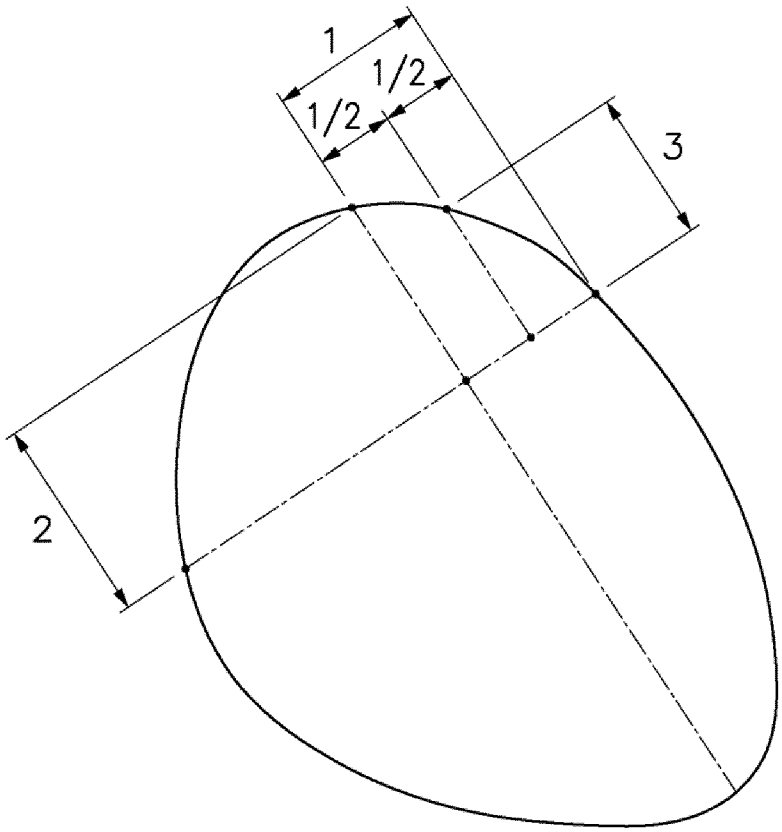


Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/062097

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B6/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J W Buchanan ET AL: "Vertebral scale system to measure canine heart size in radiographs", Journal of the American Veterinary Medical Association, 15 January 1995 (1995-01-15), pages 194-799, XP055148717, UNITED STATES Retrieved from the Internet: URL:http://www.ncbi.nlm.nih.gov/pubmed/7751220 abstract section "Materials and methods" section "Results" ----- -/--	1-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
29 October 2014	10/11/2014

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4

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	X. SÁNCHEZ ET AL: "A new method of computing the vertebral heart scale by means of direct standardisation", JOURNAL OF SMALL ANIMAL PRACTICE, vol. 53, no. 11, 1 October 2012 (2012-10-01), pages 641-645, XP055148695, ISSN: 0022-4510, DOI: 10.1111/j.1748-5827.2012.01288.x abstract section "Materials and methods" section "Results"	1-13
X	P.F. LORD ET AL: "Radiographic Heart Size and Its Rate of Increase as Tests for Onset of Congestive Heart Failure in Cavalier King Charles Spaniels with Mitral Valve Regurgitation", JOURNAL OF VETERINARY INTERNAL MEDICINE, vol. 25, no. 6, 13 September 2011 (2011-09-13), pages 1312-1319, XP055148720, ISSN: 0891-6640, DOI: 10.1111/j.1939-1676.2011.00792.x abstract section "Materials and methods"	1-13