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Renal Resistive Index in 55 Dogs with Degenerative Mitral Valve Disease

V. Chetboul, T. Daste, V. Gouni, D. Concordet, E. Trehieu-Sechi, F. Serres, J.L. Pouchelon, C.A. Germain, C. Layssol-Lamour, and H.P. Lefebvre

Background: Azotemia occurs frequently in dogs with degenerative mitral valve disease (DMVD). It could indicate changes in renal hemodynamics.

Hypothesis/Objectives: To assess the renal resistive index (RI) in dogs with DMVD, and the statistical link between heart failure class, azotemia, echo-Doppler parameters, several plasma variables, and RI.

Animals: Fifty-five dogs with naturally occurring DMVD were used (ISACHC class 1 [$n = 28$], 2 [$n = 19$], and 3 [$n = 8$]).

Methods: Observational, blinded study, performed under standardized conditions. Physical examination, renal ultrasonography, and echo-Doppler examinations were performed in awake dogs. The RI of the renal, interlobar, and arcuate arteries were measured. Plasma creatinine, urea, and N-terminal pro-B-type natriuretic peptide concentrations (NT-proBNP) were determined. Statistical links between variables and RI were tested by means of a general linear model.

Results: Although the RI of renal and arcuate arteries were unaffected by ISACHC class, the left interlobar RI increased ($P < .001$) from 0.62 ± 0.05 (mean \pm SD) in class 1 to 0.76 ± 0.08 in class 3. It was also higher ($P < .001$) in azotemic (0.74 ± 0.08) than in non-azotemic (0.62 ± 0.05) dogs. Similar findings were observed for right interlobar RI. Univariate analysis showed a positive statistical link between NT-proBNP ($P = .002$), urea ($P < .001$), creatinine ($P = .002$), urea-to-creatinine ratio ($P < .001$), left atrium-to-aorta ratio ($P < .001$), regurgitation fraction ($P < .001$), systolic pulmonary arterial pressure ($P < .001$), shortening fraction ($P = .035$), and RI.

Conclusion and Clinical Importance: In dogs with DMVD, interlobar RI increases with heart failure severity and azotemia but a cause and effect relationship remains to be established.

Key words: Azotemia; Canine; Heart failure; Kidney; Ultrasonography.

Glomerular filtration rate (GFR) is decreased in advanced, as compared to mild, degenerative mitral valve disease (DMVD) in dogs.¹ This decrease in GFR is associated with azotemia, which increases in prevalence with heart failure (HF) class (up to 71% in New York Heart Association [NYHA] class IV).¹ The most frequent cause of azotemia is abnormally high urea and not creatinine concentrations.¹ Because reabsorption of urea increases when tubular flow decreases, the more pronounced increase in plasma urea concentration could result from hemodynamic changes (ie, a

Abbreviations:

| | |
|-------------|----------------------------------------------------------------|
| ACEI | angiotensin converting enzyme inhibitor |
| Ao | aorta |
| ARJ | maximum area of the regurgitant jet signal |
| DMVD | degenerative mitral valve disease |
| EDV | left ventricular end-diastolic volume |
| EDVI | left ventricular end-diastolic volume index |
| EF | ejection fraction |
| EMITRAL | early diastolic transmitral flow velocity |
| EROA | effective regurgitant orifice area |
| ESV | left ventricular end-systolic volume |
| ESVI | left ventricular end-systolic volume index |
| GFR | glomerular filtration rate |
| HF | heart failure |
| ISACHC | International Small Animal Cardiac Health Council |
| IVSD | interventricular septal thickness in diastole |
| IVSS | interventricular septal thickness in systole |
| LA | left atrium |
| LAA | left atrium area |
| LV | left ventricle |
| LVd | left ventricular end-diastolic diameter |
| LVs | left ventricular end-systolic diameter |
| LVFWd | left ventricular free-wall in diastole |
| LVFWs | left ventricular free-wall in systole |
| NT-proBNP | N-terminal pro-B-type natriuretic peptide plasma concentration |
| NYHA | New York Heart Association |
| PUCR | plasma urea-to-creatinine ratio |
| PISA method | proximal isovelocity surface area method |
| RF | regurgitation fraction |
| RI | resistive index |
| RVd | right ventricular end-diastolic diameter |
| RVWs | right ventricular wall thickness in systole |
| SAP | systolic arterial pressure |
| SF | shortening fraction |
| SPAP | systolic pulmonary arterial pressure |
| TR | tricuspid regurgitation |

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prerenal cause) induced by decreased cardiac output, activation of neuroendocrine systems, or both.¹

The renal resistive index (RI) allows noninvasive assessment of renal vascular resistance.² Alterations in renal RI have been identified in dogs with hepatic disorders,³ hyperadrenocorticism,⁴ diabetes mellitus,⁴ renal diseases,⁵ hypoadrenocorticism,⁶ and experimentally induced anemia.⁷ Interestingly, RI is increased in human cardiac patients,⁸ but links between cardiac disease and RI have never been documented in dogs.

The purpose of this study therefore was to measure RI in dogs with naturally occurring DMVD, and to determine the links between HF class, azotemia, echo-Doppler parameters, several plasma variables (urea, creatinine, N-terminal pro-B-type natriuretic peptide plasma concentration [NT-proBNP] and plasma urea-to-creatinine ratio [PUCR]) and RI.

Materials and Methods

Study Design

The study was observational, blinded, and performed under standardized conditions. Overnight-fasted dogs underwent physical examination, blood pressure measurement, ECG, echocardiography, renal ultrasonography, and blood collection, successively on the same day.

Dogs

Dogs were prospectively recruited. Client-owned dogs with DMVD and body weight ≤ 20 kg were enrolled. The body weight criterion was based on the fact that dogs with DMVD weighing >20 kg have been shown to have a 5.8 higher chance of developing decreased shortening fraction (SF), increased end-diastolic volume index, atrial fibrillation, and ventricular arrhythmias than dogs with body weight ≤ 20 kg.^{9,10} Plasma creatinine concentration also can be affected by body size in dogs.⁴ Exclusion criteria were other cardiac diseases, neoplasia, acute renal failure, and treatment with potentially nephrotoxic drugs. Diagnosis of DMVD was performed, as previously described.¹¹ Dogs were included only if the color-flow jet of systolic mitral insufficiency was adequate for assessment of mitral regurgitation by the proximal isovelocity surface area (PISA) method.¹² Dogs with DMVD were categorized according to the International Small Animal Cardiac Health Council¹³ (ISACHC) classification. Current treatment for each dog was recorded.

Echocardiographic and Doppler Examination

Conventional echo-Doppler examinations^b were performed in awake dogs, as previously validated.¹⁴ Operators were trained and blinded to other results.

Left ventricular end-diastolic and end-systolic diameters (LVDD, LVDs), left ventricular free-wall and interventricular septal thickness in diastole and systole (LVFWd, LVFWs, IVSd, IVSs, respectively) were measured by 2-dimensional (2D) guided M-mode echocardiography.¹⁵ The SF then was calculated. The aorta (Ao) and the left atrial (LA) dimensions were measured by a 2D-echocardiographic method.¹⁴

Left ventricular end-systolic and end-diastolic volumes (ESV and EDV, respectively) were assessed by applying the Simpson's derived planimetric method by the left apical 4-chamber view, as previously validated.^{c,11} These volumes were used to calculate the

LV ejection fraction (EF). They also were indexed to body surface area (ESVI and EDVI, respectively).¹⁶

Mitral regurgitation was assessed by the color Doppler mapping and PISA methods, as previously described and validated.¹² The maximum area of the regurgitant jet signal (ARJ)/LA area (LAA) ratio, the regurgitation fraction (RF, corresponding to the percentage of stroke volume ejected into the LA during systole), and the effective regurgitant orifice area (EROA) were calculated.¹²

When tricuspid regurgitation (TR) was identified, peak-systolic TR velocity was used to calculate systolic pulmonary arterial pressure (SPAP).¹⁷ The transmitral-peak-velocity of early and late diastolic flows (EMITRAL and late diastolic transmitral flow velocity waves, respectively) also were measured.

Renal Ultrasonography

Renal ultrasonography of the 2 kidneys was performed by validated operators (see below) by an ultrasound unit^d with a 7.5 MHz linear phase-array transducer. Operators were blinded to other results. Unsedated dogs were gently restrained in lateral recumbency. A morphometric examination was performed. Renal length and height were measured on the longitudinal axis, and renal width and height were measured on the transverse axis. Arterial and venous flows were visualized by color Doppler examination. Once visualized, a pulsed-wave recording was performed on the renal artery (near its aortic origin), the interlobar artery (which crosses the medulla from renal sinus to cortico-medullary junction), and the arcuate artery (at the cortico-medullary junction). The RI was calculated by measuring peak-systolic and end-diastolic flow velocities according to the following formula:

$$RI = (\text{peak-systolic flow velocity} - \text{end-diastolic flow velocity}) / \text{peak-systolic flow velocity}.$$

Morphometric and Doppler measurements were repeated 3 times. The mean of the 3 measurements was used for statistical analysis.

To determine within-day variability for the 2 investigators and the above renal ultrasonographic variables, 3 examinations were performed on 4 healthy adult Beagle dogs at 3 nonconsecutive times on the same day. Each variable was measured 3 times during each ultrasonographic examination, by the same frame, and mean values were used to calculate variability.

Blood Pressure Measurement

Systolic arterial blood pressure (SAP) was measured in awake dogs gently restrained in lateral recumbency, by the Doppler method^c with the inflatable cuff placed on the tail. As recommended,¹⁸ several measurements were taken over 5–10 minutes to obtain the average of 5 values from a stable set of readings and the mean was used for the statistical analyses.

Blood Sample Collection and Assays

Blood samples (5 mL in a lithium-heparinized tube and 2 mL in an EDTA tube) were obtained and centrifuged ($3000 \times g$ for 10 minutes at 4°C). Heparinized and EDTA plasma were stored at -20°C and -70°C , respectively. Plasma concentrations of the following analytes: glucose, urea (urea [mg/dL] = blood urea nitrogen [mg/dL] $\times 2.14$), creatinine, potassium, chloride, calcium, total proteins, phosphate, triglycerides, cholesterol, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and creatinine kinase were assayed, by the same analyzer.^f The plasma urea-to-creatinine ratio then was calculated by dividing the plasma urea concentration expressed in mg/dL by the plasma creatinine expressed in mg/dL. Dogs were considered

azotemic if either plasma creatinine or urea was above or equal to the upper limit of the reference interval (i.e., 133 $\mu\text{mol/L}$ [1.5 mg/dL] for creatinine and 10.9 mmol/L [66 mg/dL] for urea).

NT-proBNP concentration was measured by means of EDTA-potassium samples^g and a commercially available canine-specific assay,^h as previously published.^{19,i}

The operators performing the assays were blinded to the patient's information.

Statistical Analysis

All statistical analyses were performed by means of a computer software.^j Data are expressed as mean \pm SD.

The following general linear model was used to assess the measurement variability of each renal echographic variable for each investigator¹⁴:

$$Y_{ijk} = \mu + \text{Time}_j + \text{Dog}_k + (\text{Time} * \text{Dog})_{jk} + \varepsilon_{ijk}$$

where Y_{ijk} was the i th value measured for dog k at time j , μ was the general mean, Dog_k was the effect of dog k , $(\text{Time} * \text{Dog})_{jk}$ the interaction term between time and dog effects, and ε_{ijk} was the model error.

The SD of the within-day variability was determined from the square root of the mean square of the time effect. The corresponding coefficient of variation (CV) was determined by dividing the SD value by the overall mean. A Chi-squared test was performed to compare sex, breed, and treatment between groups. Left and right interlobar RI values were compared in each class by a paired t -test. The normality of residuals was tested with a Kolmogorov-Smirnov test.

The statistical link between ISACHC class, azotemia, and all of the tested variables was assessed by an analysis of variance. Assessment between groups was performed by multiple comparisons with Tukey adjustment. The statistical link between each covariable statistically affected by ISACHC class and RI was tested by means of the following general linear model:

$$\text{RI} = \mu + a \times \text{variable} + \varepsilon$$

where μ is the mean, a is the regression coefficient for the variable, and ε is the model error.

$P < .05$ was considered significant. Adjusted R^2 values were used to compare the different statistically significant models. Stepwise regression analysis with a P -value of .20 to enter and a P -value of .10 to remove was performed for the left and right interlobar RI.

Table 1. Characteristics of the 55 dogs with degenerative mitral valve disease according to ISACHC classes.

| Characteristics | Population ($n = 55$) | ISACHC Class | | | P -value |
|----------------------------------|----------------------------|---------------------------------------|---------------------------------------|------------------------------------------|------------|
| | | 1 ($n = 28$) | 2 ($n = 19$) | 3 ($n = 8$) | |
| Sex | | | | | |
| Male | 39 (70.9%) | 21 (75%) | 14 (73.7%) | 4 (50%) | .369 |
| Female | 16 (29.1%) | 7 (25%) | 5 (26.3%) | 4 (50%) | |
| Age (years) | 10.9 \pm 3.7 [2.2–17] | 9.4 \pm 3.6 ^a [2.2–14] | 11.9 \pm 3.6 ^b [8–17] | 13.8 \pm 1.0 ^b [12.5–15] | .003 |
| (mean \pm SD, [range]) | | | | | |
| Body weight (kg) | 9.7 \pm 4.3 [1.4–20] | 10.9 \pm 5.0 [1.4–20] | 8.6 \pm 2.6 [3.6–15] | 8.2 \pm 4.2 [3–16] | .101 |
| (mean \pm SD, [range]) | | | | | |
| Breed | | | | | |
| Poodle | 9 (16.4%) | 3 (10.7%) | 4 (21.1%) | 2 (25%) | .782 |
| CKC Spaniel | 15 (27.3%) | 9 (32.1%) | 6 (31.6%) | 0 | |
| Yorkshire Terrier | 4 (7.3%) | 1 (3.6%) | 2 (10.5%) | 1 (12.5%) | |
| Bichon | 3 (5.5%) | 1 (3.6%) | 1 (5.3%) | 1 (12.5%) | |
| Cross breed | 9 (16.4%) | 4 (14.3%) | 3 (15.8%) | 2 (25%) | |
| Other breeds | 15 (27.3%) | 10 (35.7%) | 3 (15.8%) | 2 (25%) | |
| Treatments | | | | | |
| ACEI | 36 (65%) | 14 (50%) | 15 (79%) | 7 (88%) | .011 |
| Spironolactone | 18 (33%) | 2 (7%) | 9 (47%) | 7 (88%) | |
| Furosemide | 15 (27%) | 1 (4%) | 6 (32%) | 8 (100%) | |
| Pimobendan | 1 (2%) | 0 | 1 (5%) | 0 | |
| Theophylline | 5 (9%) | 1 (4%) | 3 (16%) | 1 (13%) | |
| Others | 8 (15%) | 1 (4%) | 4 (21%) | 3 (16%) | |
| Heart rate (bpm) | 129 \pm 29 [70–210] | 120 \pm 18 [80–165] | 138 \pm 33 [90–210] | 139 \pm 40 [70–190] | .060 |
| (mean \pm SD, [range]) | | | | | |
| SAP (mmHg) | 145 \pm 18 [100–185] | 150 \pm 16 [110–185] | 140 \pm 17 [100–160] | 137 \pm 19 [110–170] | .056 |
| (mean \pm SD, [range]) | | | | | |
| NT-proBNP (pmol/L) | 1043 \pm 1260 [174–4890] | 309 \pm 127 ^a [174–700] | 921 \pm 571 ^b [349–2273] | 3561 \pm 1291 ^c [1871–4890] | <.001 |
| Urea (mmol/L) | 8.9 \pm 9.0 [1.3–47.7] | 5.4 \pm 2.7 ^a [2.5–16.7] | 8.8 \pm 6.8 ^a [1.3–31.9] | 21.7 \pm 15.4 ^b [9.3–47.7] | <.001 |
| Creatinine ($\mu\text{mol/L}$) | 89 \pm 44 [53–327] | 76 \pm 21 ^a [53–137] | 84 \pm 23 ^a [55–128] | 144 \pm 88 ^b [83–327] | <.001 |
| PUCR | 51 \pm 34 [12–214] | 39 \pm 19 ^a [19–111] | 55 \pm 43 ^{a,b} [12–214] | 82 \pm 35 ^b [51–156] | .004 |

ACEI, angiotensin converting enzyme inhibitors; bpm, beats per minute; CKC, Cavalier King Charles Spaniel; ISACHC, International Small Animal Cardiac Health Council; PUCR, plasma urea-to-creatinine ratio (mg/dL)/(mg/dL); NT-proBNP, N-terminal pro-B-type natriuretic peptide plasma concentration; SAP, systolic arterial pressure.

a, b, c: when the superscripts are different, the difference between groups is statistically significant ($P < .05$).

Results

Study Population

Fifty-five dogs (28 [50.9%] in ISACHC class 1, 19 [34.5%] in class 2, and 8 [14.5%] in class 3) were included in the study (Table 1). Dogs from class 1 were younger than those from classes 2 and 3. Body weight, heart rate, and SAP were not statistically different among ISACHC classes. No chronic kidney disease was diagnosed in any dog. No dog had any other concomitant diagnosed disease at the time of the study, except 1 dog in class 2 for which hypothyroidism had been diagnosed. Nevertheless, this dog was under treatment with levothyroxine at the time of the study.

Thirty-eight of the 55 dogs (69.1%) received at least 1 treatment at the time of diagnosis. Dogs in class 3 received higher doses ($P < .001$) of furosemide (3.0 ± 2.3 mg/kg/day) than the only dog in class 1 (1 mg/kg/day) or those in class 2 (0.8 ± 1.6 mg/kg/day).

Validation of Renal Ultrasonography

Within-day CVs for the renal ultrasonographic and Doppler measurements are presented in Table 2. Maximal values for renal, interlobar, and arcuate RI were 14.7%, 17.2%, and 25.4%, respectively.

Links between ISACHC Class and Tested Variables

No departure of normality was observed for any of the tested variables. The LA/Ao ratio increased signifi-

cantly with HF class as well as SF, EMITRAL, ARJ/LAA, EROA, RF, SPAP, and EDVI (Table 3).

Right and left interlobar RI measurements were missing for 9 and 3/55 dogs, respectively, because the dogs were not cooperative during imaging. Interlobar RI was the only renal ultrasonographic variable significantly affected by ISACHC class (Table 4).

Table 2. Coefficients of variation (%) for within-day renal morphometric and Doppler ultrasonography values measured by the 2 investigators in 6 healthy Beagles.

| | Investigator 1 | Investigator 2 |
|---------------------|----------------|----------------|
| Left Kidney | | |
| Length-long | 4.6 | 7.6 |
| Height-long | 8.5 | 5.6 |
| Width-trans | 5.1 | 15.7 |
| Height-trans | 4.9 | 5.4 |
| RI renal | 4.5 | 14.7 |
| RI interlobar | 13.0 | 16.7 |
| RI arcuate | 18.3 | 9.9 |
| Right Kidney | | |
| Length-long | 1.8 | 17.5 |
| Height-long | 1.8 | 17.3 |
| Width-trans | 18.9 | 4.8 |
| Height-trans | 9.9 | 12.9 |
| RI renal | 4.2 | 9.3 |
| RI interlobar | 7.3 | 17.2 |
| RI arcuate | 25.4 | 15.8 |

Long, longitudinal axis; trans, transversal axis; RI, resistive index.

Table 3. Cardiovascular variables in 55 dogs with degenerative mitral valve disease according to ISACHC classes.

| Variable | Unit | Total | ISACHC Class | | | P |
|------------------------|---------------------------------|-------------|--------------------------|---------------------------|--------------------------|-------|
| | | | 1 (n = 28) | 2 (n = 19) | 3 (n = 8) | |
| LA/Ao | – | 1.48 ± 0.65 | 1.07 ± 0.28 ^a | 1.76 ± 0.69 ^b | 2.27 ± 0.29 ^c | <.001 |
| IVSd | mm | 7.0 ± 1.5 | 7.2 ± 1.7 | 6.8 ± 1.2 | 6.9 ± 1.4 | .633 |
| LVd | mm | 34.7 ± 6.8 | 33.3 ± 6.5 | 35.4 ± 6.9 | 37.8 ± 7.1 | .229 |
| LVFWd | mm | 7.2 ± 1.5 | 7.5 ± 1.8 | 7.0 ± 1.2 | 6.5 ± 1.0 | .251 |
| IVSs | mm | 11.7 ± 2.1 | 11.5 ± 2.1 | 11.5 ± 1.9 | 13.2 ± 2.0 | .110 |
| LVs | mm | 19.1 ± 4.7 | 19.4 ± 4.4 | 19.1 ± 4.4 | 18.2 ± 6.7 | .816 |
| LVFWs | mm | 11.9 ± 2.4 | 12.1 ± 2.9 | 11.4 ± 1.8 | 12.3 ± 2.0 | .569 |
| Shortening fraction | % | 44.9 ± 8.5 | 41.9 ± 7.6 ^a | 46.0 ± 7.5 ^{ab} | 52.6 ± 9.7 ^b | .004 |
| EMITRAL | m/s | 1.15 ± 0.46 | 0.95 ± 0.36 ^a | 1.3 ± 0.47 ^b | 1.6 ± 0.36 ^b | <.001 |
| ARJ/LAA | – | 0.81 ± 0.23 | 0.71 ± 0.26 ^a | 0.89 ± 0.15 ^b | 0.94 ± 0.11 ^b | .005 |
| EROA | cm ² | 0.09 ± 0.07 | 0.06 ± 0.04 ^a | 0.11 ± 0.08 ^b | 0.15 ± 0.09 ^b | .003 |
| Regurgitation fraction | % | 35.3 ± 16.1 | 27.3 ± 12.3 ^a | 41.4 ± 16.1 ^b | 49.1 ± 13.4 ^b | <.001 |
| SPAP | mmHg | 49.4 ± 28.9 | 39.5 ± 18.6 ^a | 51.3 ± 32.3 ^{ab} | 77.0 ± 31.9 ^b | .004 |
| ESVI | cm ³ /m ² | 18.7 ± 8.9 | 18.4 ± 8.5 | 17.0 ± 9.5 | 23.8 ± 7.9 | .190 |
| EDVI | cm ³ /m ² | 65.3 ± 21.3 | 58.1 ± 18.5 ^a | 65.8 ± 20.7 ^a | 89.5 ± 14.7 ^b | .001 |
| EF (Simpson’s method) | % | 71.1 ± 9.8 | 68.4 ± 9.6 | 74.0 ± 9.9 | 73.3 ± 8.9 | .122 |

ARJ/LAA, maximum area of the regurgitant jet signal/left atrium area ratio; EMITRAL, early diastolic transmitral flow velocity; EROA, effective regurgitant orifice area; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; IVSd, interventricular septum in diastole; IVSs, interventricular septum in systole; LA/Ao, left atrium-to-aorta ratio; LVFWd, left ventricular free-wall in diastole; LVFWs, left ventricular free-wall in systole; SPAP, systolic pulmonary arterial pressure; LVd, left ventricular end-diastolic diameter; LVs, left ventricular end-systolic diameter.

a, b, c: when the superscripts are different, the difference between groups is statistically significant ($P < .05$).

Table 4. Renal ultrasonographic and Doppler variables in 55 dogs with degenerative mitral valve disease, according to ISACHC classes.

| Kidney | Variable | Total | ISACHC Class | | | P |
|--------|------------------|-------------|--------------------------|---------------------------|--------------------------|-------|
| | | | 1 (n = 28) | 2 (n = 19) | 3 (n = 8) | |
| Right | Length (mm) | 32.2 ± 22.8 | 29.6 ± 22.9 | 30.2 ± 24.5 | 48.2 ± 11.5 | .248 |
| | Height (LS) (mm) | 17.9 ± 12.9 | 16.1 ± 12.6 | 17.3 ± 14.0 | 26.9 ± 8.4 | .245 |
| | Height (TS) (mm) | 17.2 ± 12.9 | 15.0 ± 12.5 | 17.7 ± 14.3 | 25.7 ± 9.0 | .329 |
| | Width (mm) | 19.2 ± 15.4 | 15.6 ± 14.6 | 20.9 ± 17.0 | 30.4 ± 10.2 | .203 |
| | Renal RI | 0.68 ± 0.08 | 0.71 ± 0.09 | 0.64 ± 0.05 | 0.69 ± 0.07 | .054 |
| | Interlobar RI | 0.67 ± 0.07 | 0.64 ± 0.05 ^a | 0.68 ± 0.08 ^{ab} | 0.77 ± 0.06 ^b | .004 |
| Left | Arcuate RI | 0.64 ± 0.08 | 0.64 ± 0.08 | 0.63 ± 0.08 | 0.65 ± 0.14 | .803 |
| | Length (mm) | 33.5 ± 22.3 | 35.4 ± 22.1 | 29.1 ± 24.0 | 37.9 ± 19.6 | .573 |
| | Height (LS) (mm) | 20.0 ± 13.0 | 20.5 ± 13.0 | 18.3 ± 13.9 | 22.6 ± 11.2 | .750 |
| | Height (TS) (mm) | 18.8 ± 12.8 | 19.0 ± 13.0 | 18.3 ± 13.8 | 19.8 ± 10.3 | .967 |
| | Width (mm) | 21.5 ± 14.6 | 22.1 ± 15.1 | 20.4 ± 15.6 | 22.5 ± 11.1 | .921 |
| | Renal RI | 0.69 ± 0.08 | 0.68 ± 0.08 | 0.71 ± 0.08 | 0.68 ± 0.08 | .500 |
| | Interlobar RI | 0.65 ± 0.08 | 0.62 ± 0.05 ^a | 0.67 ± 0.08 ^b | 0.76 ± 0.08 ^c | <.001 |
| | Arcuate RI | 0.65 ± 0.08 | 0.65 ± 0.10 | 0.65 ± 0.07 | 0.64 ± 0.07 | .909 |

LS, longitudinal section; RI, resistive index; TS, transversal section.

a, b, c: when the superscripts are different, the difference between groups is statistically significant ($P < .05$).

Right and left interlobar RI were significantly increased in class 3.

Plasma urea and creatinine concentrations were significantly higher in dogs from class 3 than in those from classes 1 and 2. The plasma urea-to-creatinine-ratio also was higher in dogs from class 3 than in those from class 1. Plasma NT-proBNP also increased with ISACHC class (Table 1). Other plasma variables were unaffected by HF class.

Azotemia and Other Tested Variables

Sixteen of 55 dogs (29%) were azotemic because of an abnormally high concentration of plasma urea ($n = 12$), creatinine ($n = 1$), or both ($n = 3$). Azotemic dogs were older and were receiving higher doses

of furosemide. Left atrium-to-aorta ratio, EMITRAL, EROA, RF, SPAP, interlobar RI, plasma NT-proBNP, PUCR, and triglycerides also were higher in azotemic dogs compared to nonazotemic dogs (Table 5).

Covariables Affecting Interlobar RI

Left and right interlobar RI were not statistically different within each ISACHC class. Right and left interlobar RI increased with age, furosemide dose, LA/Ao, SF, RF, SPAP, plasma NT-proBNP, plasma urea, plasma creatinine, and PUCR. Left interlobar RI also increased with ARJ/LAA, EROA, and EDVI (Table 6). The highest R^2 value was observed for urea.

Table 5. Effect of azotemic status on covariables in 55 dogs with degenerative mitral valve disease. Only statistically significant results are presented.

| Variable | Unit | Nonazotemic Dogs (n = 39) | Azotemic Dogs (n = 16) | P |
|------------------------|-----------------|---------------------------|------------------------|-------|
| Age | Year | 10.0 ± 3.7 | 13.3 ± 2.4 | .002 |
| Furosemide dose | mg/kg/day | 0.28 ± 1.0 | 2.0 ± 2.2 | <.001 |
| LA/Ao | – | 1.28 ± 0.57 | 2.00 ± 0.54 | <.001 |
| EMITRAL | m/s | 1.1 ± 0.42 | 1.4 ± 0.47 | .015 |
| EROA | cm ² | 0.08 ± 0.06 | 0.12 ± 0.08 | .043 |
| Regurgitation fraction | % | 31.2 ± 15.1 | 46.4 ± 13.7 | .001 |
| SPAP | mmHg | 43.0 ± 25.1 | 65.6 ± 32.1 | .009 |
| Right interlobar RI | – | 0.65 ± 0.06 | 0.75 ± 0.06 | <.001 |
| Left interlobar RI | – | 0.62 ± 0.05 | 0.74 ± 0.08 | <.001 |
| NT-proBNP | pmol/L | 610 ± 563 | 2648 ± 1825 | <.001 |
| Urea | mmol/L | 5.3 ± 2.2 | 18.6 ± 12.6 | <.001 |
| Creatinine | μmol/L | 75.6 ± 19.1 | 123.4 ± 68.2 | <.001 |
| PUCR | (mg/dL)/(mg/dL) | 37.1 ± 13.9 | 83.1 ± 46.7 | <.001 |
| Triglycerides | mmol/L | 0.52 ± 0.33 | 0.85 ± 0.76 | .031 |

EMITRAL, early diastolic transmitral flow velocity; EROA, effective regurgitant orifice area; LA/Ao, left atrium-to-aorta ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide plasma concentration; PUCR, plasma urea-to-creatinine ratio; RI, resistive index; SPAP, systolic pulmonary arterial pressure.

Table 6. Statistically significant models including 1 variable and affecting the right and left interlobar resistive RI tested by a general linear model ($RI = \mu + a \times \text{variable} + \varepsilon$) in a population of 55 dogs with degenerative mitral valve disease.

| Variable | Unit | a | μ | P | R ² |
|-------------------------|---------------------------------------|-----------------------|-------|-------|----------------|
| Right interlobar artery | | | | | |
| Age | Year | 0.007 | 0.597 | .040 | 0.093 |
| Furosemide dose | mg/kg/day | 0.026 | 0.654 | <.001 | 0.395 |
| LA/Ao | – | 0.072 | 0.568 | <.001 | 0.316 |
| Shortening fraction | % | 0.003 | 0.528 | .028 | 0.109 |
| Regurgitation fraction | % | 0.002 | 0.607 | .011 | 0.153 |
| SPAP | mmHg | 0.001 | 0.635 | .034 | 0.106 |
| NT-proBNP | pmol/L | 0.031 $\cdot 10^{-3}$ | 0.636 | .002 | 0.288 |
| Urea | mmol/L | 0.007 | 0.617 | <.001 | 0.450 |
| Creatinine | $\mu\text{mol/L}$ | 0.001 | 0.572 | .002 | 0.237 |
| PUCR | $\text{mg.dL}^{-1}/\text{mg.dL}^{-1}$ | 0.002 | 0.593 | <.001 | 0.390 |
| Left interlobar artery | | | | | |
| Age | Year | 0.010 | 0.540 | <.001 | 0.222 |
| Furosemide dose | mg/kg/day | 0.030 | 0.631 | <.001 | 0.390 |
| LA/Ao | – | 0.071 | 0.548 | <.001 | 0.335 |
| Shortening fraction | % | 0.003 | 0.532 | .035 | 0.067 |
| ARJ/LAA | – | 0.102 | 0.571 | .028 | 0.075 |
| EROA | cm^2 | 0.511 | 0.607 | .001 | 0.191 |
| Regurgitation fraction | % | 0.003 | 0.558 | <.001 | 0.309 |
| SPAP | mmHg | 0.001 | 0.590 | <.001 | 0.236 |
| EDVI | cm^3/m^2 | 0.001 | 0.575 | .024 | 0.080 |
| NT-proBNP | pmol/L | 0.034 $\cdot 10^{-3}$ | 0.613 | <.001 | 0.386 |
| Urea | mmol/L | 0.006 | 0.601 | <.001 | 0.473 |
| Creatinine | $\mu\text{mol/L}$ | 0.001 | 0.559 | <.001 | 0.358 |
| PUCR | $\text{mg.dL}^{-1}/\text{mg.dL}^{-1}$ | 0.001 | 0.600 | <.001 | 0.209 |

ARJ/LAA, maximum area of the regurgitant jet signal/left atrium area ratio; EDVI, end-diastolic volume index; EROA, effective regurgitant orifice area; LA/Ao, left atrium-to-aorta ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide plasma concentration; PUCR, plasma urea-to-creatinine ratio; RI, resistive index; SPAP, systolic pulmonary arterial pressure; μ , mean; a, regression coefficient of the variable; ε , the residual corresponding to the model error.

The stepwise regression analysis provided the following 2 models:

Left interlobar RI = $-0.001 \times \text{Heart rate (bpm)} + 0.031 \times \text{LA/Ao} + 0.001 \times \text{SPAP (mmHg)} + 0.004 \times \text{Urea (mmol/L)} + 2.2 \cdot 10^{-4} \times \text{Creatine Kinase (U/L)}$, $R^2 = 0.643$

Right interlobar RI = $-0.001 \times \text{Heart rate (bpm)} + 0.013 \times \text{Urea (mmol/L)} + 0.014 \times \text{Sodium (mmol/L)} - 0.004 \times \text{Chloride (mmol/L)}$, $R^2 = 0.676$

Discussion

This present study indicates that interlobar RI increases with HF severity and with azotemia. The

studied population was representative of dogs with DMVD.²⁰ As previously described, age, plasma urea, creatinine, NT-proBNP, and PUCR increased with ISACHC class.^{1,11,12,17}

Only interlobar RI was affected by HF severity. No difference was observed between left and right interlobar RI within each ISACHC class, as previously reported.^{4,5} Interlobar RI values in class 1 dogs were consistent with those reported in normal dogs.^{5,7,21,22} Conversely, dogs in class 3 had similar interlobar RI to those of dogs with renal dysplasia (0.73 ± 0.006) or acute kidney injury (0.72 ± 0.08).⁵ The right interlobar RI increased significantly by 22% only between classes 1 and 3. A significant increase in left interlobar RI was observed between classes (ie, 20% between classes 1 and 3, 6% between classes 1 and 2, and 13% between classes 2 and 3). Within-day variability for left interlobar RI measurement for the 2 investigators, however, was 13.0% and 16.7%. Consequently, a clinical interpretation of the increase in left interlobar RI was only possible between classes 1 and 3. The intrinsic measurement variability was higher than that described in humans (CV = 4.8–7.1%),^{23,24} probably attributable to the difficulty of obtaining such measurements in awake dogs. The potential factors of variation explaining such variability could be the handling and position of the animal, probe application, and direct measurement of peak-systolic and end-diastolic velocities by the investigator. Surprisingly, only interlobar RI showed statistically significant differences according to the ISACHC class, whereas renal and arcuate RI values remained unchanged. Our data do not allow such discrepancies to be explained. In humans, the most frequently measured RI is interlobar RI based on 1 report,²⁴ which indicated that interlobar RI was the parameter with the most consistent results and should be preferred in clinical situations. In our study, within-day CV for measurement of renal RI was better than that of interlobar RI. Therefore, the lack of difference observed cannot be explained by the intrinsic variability of the measurement per se. On the other hand, this latter finding could provide a potential explanation for arcuate RI.

Such differences also could mean that hemodynamic alterations differ according to the level of renal vasculature. In humans, discrepancies also have been observed according to the site of measurement of RI in different clinical settings.^{25–27} Interpretation of an increase in interlobar RI may be misleading, because RI indeed is dependent on vascular compliance, resistance, and cross-sectional area of the distal vascular bed.^{2,28} In humans, vascular compliance may be altered with age, medication, and renal diseases. Nevertheless, in the present study, interlobar RI appeared to be affected by markers of DMVD severity and prognosis (LA/Ao, NT-proBNP),^{29,30} and by functional markers of renal function (urea, creatinine, and PUCR). Moreover, based on R² value, urea alone explained almost 50% of the variability of the left and right interlobar RI. The R² values were only very slightly increased by models with 2 variables. A

potential confounding factor could be treatment differences among ISACHC classes. Most (>79%) of the dogs in ISACHC classes 2 and 3 received an angiotensin converting enzyme inhibitor (ACEI). In class 1, only 50% of the dogs were treated with ACEI. Although ACEI have a limited effect on renal function in dogs with cardiac disease,^{31,32} they may affect intrarenal hemodynamics. In dogs with experimental chronic kidney disease, enalapril preferentially induced vasodilatation of the efferent arteriole.³³ Moreover, infusion of angiotensin II increases renal vascular resistance in rats.³⁴ Thus, a decrease and not an increase in interlobar RI would have been expected as a consequence of ACEI treatment.

Furosemide was given to 4%, 32%, and 100% of the dogs in classes 1, 2, and 3, respectively. This class-dependent difference in furosemide treatment could explain in part the changes in renal function and interlobar RI. Azotemia caused by increased plasma urea concentration has been described in dogs with cardiac disease treated with both furosemide and enalapril.³⁵ Treatment with furosemide also decreases GFR in healthy dogs.³⁶ Moreover, tubuloglomerular feedback, which is a major renal blood flow autoregulating system, is blocked by furosemide.^{37,38} In humans, furosemide has no effect on normal kidney RI but increases RI in kidneys with ureteral obstruction.³⁹ In dogs, furosemide has no effect on RI in kidneys with ureteral obstruction.⁴⁰ However, the effects of long-term furosemide administration on kidney function in dogs with cardiac disease have never been investigated. In our study, furosemide-induced changes in interlobar RI cannot be excluded because the administered dose was associated ($P < .001$, $R^2 = 0.39-0.40$) with an increase in interlobar RI.

The final model obtained with stepwise regression for left and right interlobar RI had R^2 values of 0.64 and 0.68, respectively, indicating that the variables tested in this study do not explain the total variability observed for RI. Urea was a statistically significant variable in the models indicating again that RI and changes in plasma urea concentration occur in parallel. Interestingly, when heart rate increased, RI decreased. This result appears paradoxical because it has been reported that heart rate >140 bpm is an indicator of more severe cardiac disease.⁴¹ However, a similar relationship, as identified here, between RI and heart rate has been reported in humans.^{42,43} The other variables included in the models differ according to the side (left versus right) and their clinical relevance is more difficult to explain here, although LA/Ao⁴¹ and SPAP^{11,44} have been reported as prognostic indicators in DMVD.

In conclusion, canine DMVD is associated with increased interlobar RI according to HF class. Further investigations are now required to document the underlying pathophysiologic mechanisms responsible for such class-dependent RI changes and to determine their impact on prognosis and medical management in dogs with DMVD.

Footnotes

^aCraig AJ, Seguela J, Queau Y, et al. Redefining the reference interval for plasma creatinine in dogs: effect of age, gender, body weight, and breed. *J Vet Intern Med* 2006;20:740 (abstract)

^bVivid 7, General Electric Medical System, Waukesha, WI

^cEchopac Dimension, General Medical System, Waukesha, WI

^dLogic 5 Expert – Scill Healthcare, General Electric Medical System, Fairfield, CT

^e811-BL, Parks Medical Electronics, Inc, Aloha, OR

^fVitros 250 chemistry system, Ortho-Clinical Diagnostics, Johnson & Johnson, Illkirch Graffenstaden, France

^gBiomedica Gruppe, Divischgasse 4, A-1210 Vienne, Austria

^hVetsign Canine CardioScreen NT-proBNP, Guildhay, Ltd, Surrey, UK

ⁱZieba M, Beardow A, Carpenter C, et al. Analytical validation of a commercially available canine N-terminal prohormone Brain Natriuretic Peptide elisa. *J Vet Intern Med* 2008;22:717 (abstract)

^jSystat, version 12.00.08, SPSS Inc, Chicago, IL

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