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Use of a serum-based glomerular filtration rate prediction equation to assess renal function by age, sex, fasting, and health status in bottlenose dolphins (*Tursiops truncatus*)

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ABSTRACT

Glomerular filtration rate (GFR) is a direct measurement of renal function. Although clearance tests using 24-h urine collection or blood sample series are gold standards for measuring GFR, serum-based prediction of GFR based upon the Modification of Diet in Renal Disease (MDRD) Study equation is acceptable for routine use in human adults. The purpose of our study was to assess the ability for a modified MDRD Study equation to predict expected changes in GFR in bottlenose dolphins (*Tursiops truncatus*) using a healthy dolphin population represented by 1,103 routine serum samples collected from 50 dolphins of all age groups, years 1998–2005. Predicted GFR was also calculated from serum collected from a 32-yr-old male dolphin with end-stage renal disease. The dolphin-adjusted MDRD equation predicted GFR changes in our population that paralleled what has previously been reported in other mammals, including decreasing predicted GFR with age ($P < 0.01$), higher predicted GFR in dolphins that had recently eaten ($P < 0.01$), and rapidly decreasing predicted GFR in the animal with end-stage renal disease. We conclude that a serum-based GFR prediction equation may be a feasible means of detecting and tracking renal function in bottlenose dolphins.

Key words: bottlenose dolphin, *Tursiops truncatus*, glomerular filtration rate, kidney, renal, renal disease, GFR prediction equation.

Glomerular filtration rate (GFR) is a direct measurement of renal function. Current gold standards for measuring GFR are clearance of specific filtration markers either in the urine over a 24-h period (Hjorth *et al*. 2002) or in a series of blood samples over several hours (Frennby and Sterner 2002). There are, however, limited studies assessing true GFR in *Tursiops truncatus* (bottlenose dolphins). Inulin clearance studies conducted by Malvin and Rayner (1968) on two female dolphins demonstrated GFR ranging from 131 to 465 mL/min, and Ridgway (1972*a*) reported similar creatinine clearance rates in six bottlenose dolphins using 24-h measurement of urine creatinine. Though renal disease has been recognized in bottlenose dolphins (Ridgway and Schroeder 1989, Miller 1994, Reidarson and McBain 1994), routine assessment of renal function in marine mammals *via* 24-h urine collection or blood sample series using contrast media is tedious and difficult.

The Modified Diet in Renal Disease (MDRD) Study equation is a serum-based algorithm used to predict GFR in adult humans. Use of this equation to detect and monitor renal function is currently recommended by the National Institute of Diabetes and Diseases of the Kidney, the National Kidney Foundation, and the American Society of Nephrology (Stevens and Levey 2004, Stevens *et al*. 2007). The MDRD Study equation has been determined to be a more sensitive indicator of GFR than creatinine clearance measured by urine collection (Levey *et al*. 1999, Lamb *et al*. 2003) or by the Cockcroft-Gault equation (Kuan *et al*. 2005, Gerchman *et al*. 2007).

Validation of a serum-based predictor of GFR in bottlenose dolphins would greatly improve the ability to assess the impact and progression of renal disease in marine mammals. Although it is not assumed that dolphins and humans have identical renal physiology, development of a dolphin-specific GFR prediction equation may be possible by adapting the MDRD Study equation.

As an initial approach to validating a serum-based GFR prediction equation in bottlenose dolphins, we assessed a simplified, dolphin-adjusted MDRD Study equation for prediction of expected GFR changes based upon age, sex, and fasting status in a healthy dolphin population. Additionally, we applied the dolphin-adjusted MDRD Study equation to retrospective data from a dolphin that died from end-stage renal disease. Results from our study population were compared with those reported in other mammals to assess the ability of the dolphin-adjusted MDRD equation to predict GFR in bottlenose dolphins.

MATERIALS AND METHODS

Sample Collection

We conducted retrospective analysis of serum clinical biochemistry data that were originally collected as part of the United States Navy Marine Mammal Program's (MMP) preventive medicine program or a clinical work up by an attending veterinarian. In general, blood samples were collected by venipuncture from animals trained to voluntarily present their tail for sampling or using behavioral conditioning out of the water on a foam mat during a routine physical exam. Blood samples were collected using a 20 or 21 gauge, 1.5 in. Vacutainer needle (Becton Dickinson VACUTAINER Systems, Rutherford, NJ). Blood was collected into a Vacutainer serum separator tube (SST) tube for serum chemistries. Samples were chilled for 30 min and centrifuged within 2 h. Centrifugation was performed at 3,000 rpm at 21°C for 10 min. Fibrin clots were removed and serum was transferred to a 5-mL plastic

submission tube. All samples were sent on ice via courier to a clinical reference laboratory.

All samples were submitted to Quest Diagnostic Laboratories (San Diego, California), a laboratory with an effective quality control program and more than 20 yr of experience in the analysis of dolphin blood. Automated analyses were used by Quest, including the Coulter LH 1500 Series (Beckman Coulter, Inc., Fullerton, CA) for hematology and the Olympus AU600 (Olympus America Inc., Center Valley, PA) for serum chemistry analyses.

Simplified, Dolphin-Adjusted GFR Prediction Equation

The current MDRD Study equation used in human populations is GFR (mL/min/1.73 m^2) = 186 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × (0.742 if female) × (1.180 if black) (Stevens *et al*. 2006). Due to the unknown effects of age and sex on dolphin GFR, these qualifiers, as well as ethnicity, were removed from the dolphin-adjusted equation. The MDRD Study equation uses 1.73 m^2 as the accepted average body surface area (BSA) for adult humans. Adult bottlenose dolphins, however, are larger than humans; as such, we applied a 1.61 constant multiplier. This constant was based upon an average BSA of 2.78 m^2 previously calculated among three in-house adult dolphins (2.78 m^2 dolphin BSA/1.73 m^2 human BSA = 1.61). The final simplified, dolphin-adjusted MDRD Study equation used to predict GFR in our study was as follows: GFR (mL/min/2.78 m^2) = 186 × serum creatinine$^{-1.154}$ × 1.61.

Study Population

The dolphin-adjusted MDRD equation was applied to retrospective serum creatinine data from a dataset including 1,103 blood samples from 50 healthy bottlenose dolphins, years 1998–2005. For the purposes of this study, healthy animals were defined as animals without a follow up clinical blood sample within 14 d, no known chronic or acute illness, and not receiving antimicrobial treatment or cimetidine. Only routinely collected and non-hemolyzed samples were included. Ages were divided into the following categories: 1–5 yr, >5–10 yr, >10–30 yr, and >30 yr. Although it has been recognized that high variation in blood analyte values may exist during ages 0–3 yr (Noren *et al*. 2002), we were unable to statistically parse out these ages due to a relatively low number of routine, healthy blood samples collected from neonates and young calves.

The case study dataset involved retrospective serum creatinine data from a 32-yr-old male dolphin that died from end-stage renal disease secondary to chronic nephrolithiasis.

Statistics

All data were analyzed using SAS software (Release 8e; SAS Institute, Inc., Cary, NC). For the dataset from healthy animals, mean differences in estimated GFR were analyzed by age, sex, and fasting status using an analysis of covariance *via* a general linear model that adjusted for varying numbers of serum samples among animals (PROC GLM; CLASS age sex fasting; MODEL GFR = [age sex fasting]; LSMEANS [age sex fasting]). A Type I SS *P* value < 0.01 was considered significant for analyses of covariance; for analyses involving comparisons of more than two categories (*e.g.*,

four age groups), a *post hoc* Scheffe's test was conducted to assess significance of variance among each of the categories. Least squares means controlling for covariates are reported.

Simple linear regressions were used to analyze estimated GFR over time in a dolphin that died from end stage renal disease. Significance was defined as $P < 0.01$.

RESULTS

Predicted GFR in a Healthy Population by Age, Sex, and Fasting Status

Among serum data from 1,103 samples analyzed from 50 healthy bottlenose dolphins, the median predicted GFR was 188 mL/min/2.78 m^2 (range 95–387 mL/min/2.78 m^2) and the mean was 197 mL/min/2.78 m^2 (SD 45 mL/min/2.78 m^2). Age, sex, and fasting status were all significant predictors of GFR using the dolphin-adjusted MDRD Study equation (Table 1); females, younger animals, and animals that were recently fed fish had a higher predicted GFR compared to males, older animals, and animals that were not fed overnight, respectively. Upon conducting *post hoc* multiple comparisons among the four age groups, dolphins aged 1–5 yr were more likely to have higher predicted GFR compared to dolphins in all three older age groups, and dolphins aged >5–10 yr were more likely to have higher predicted GFR compared to dolphins aged >10 –30 yr.

Case Study

In 2005, a 32-yr-old male Atlantic bottlenose dolphin with chronic nephrolithiasis died due to irreversible, end-stage renal disease. The animal had undergone 33 d of medical management to address the following abnormalities related to renal disease:

Table 1. Comparisons of mean predicted glomerular filtration rate (GFR), within age, sex, and feeding status groups, using a dolphin-adjusted MDRD study equation in a healthy bottlenose dolphin (*Tursiops truncatus*) population.

Study categories by group	n (1,103)	Least-squares mean predicted GFR (mL/min/2.78 m^2)	In-group comparisons of mean predicted GFR by category (P-value)[a]
Age group			<0.0001
1–5 yr	102	247	
>5–10 yr	81	215	
>10–30 yr	654	192	
>30 yr	266	190	
Sex			<0.0001
Female	530	222	
Male	573	200	
Feeding status			<0.0001
Not fed for >12 h	592	202	
Recent fish meal	511	219	

[a]Comparison of mean predicted GFR within each group were determined using Type I SS *P*-values controlling for covariates; comparisons among multiple age groups also included a *post hoc* Scheffe's test.
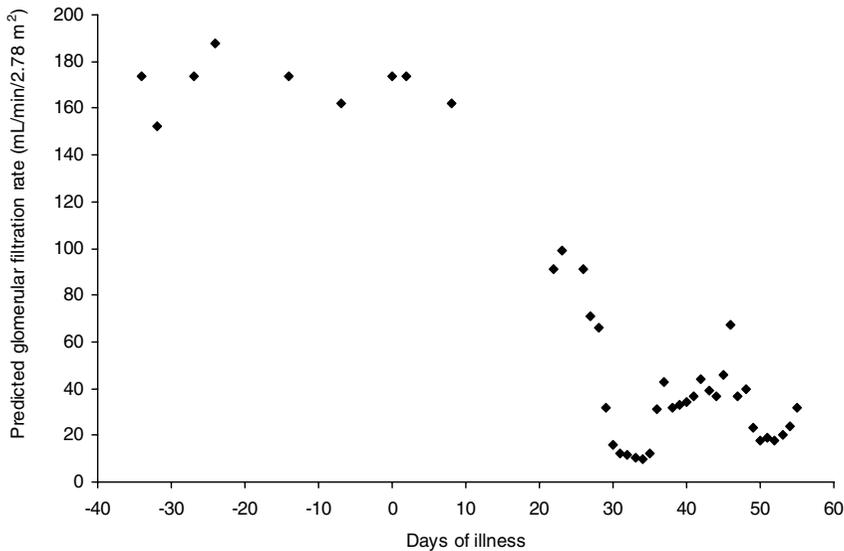
Figure 1. Serum-based predicted glomerular filtration rate over a 55-d period using a dolphin-adjusted MDRD equation by days ill in an adult male Atlantic bottlenose dolphin (*Tursiops truncatus*) with end-stage renal disease.

dehydration, profound azotemia, metabolic acidosis, hypernatremia, hyperchloremia, hyperphosphatemia, hyperlipidemia, a mature neutrophilic leukocytosis, and anemia. Throughout the course of treatment, the animal was partially anorexic, cachexic, and lethargic. Antemortem diagnostics to confirm renal disease included cutaneous diagnostic ultrasound, renal scintigraphy, and percutaneous renal biopsy. Chronic, progressive renal nephrolithiasis had been previously confirmed with renal cutaneous diagnostic ultrasound.

A total of 77 fasted serum samples were collected from this animal during 10 yr before the onset of end stage renal disease (June 1993 through March 2003, ages 20–30 yr). The median predicted GFR using the dolphin-adjusted MDRD Study equation for this animal was 152 mL/min/2.78 m^2 (range, 81–203 mL/min/2.78 m^2). A sharp drop in predicted GFR, from 162 mL/min/2.78m^2 on 18 May 2005 to 12 mL/min/2.78 m^2 on 23 May 2005, was apparent during end stage renal disease (Fig. 1).

DISCUSSION

Using a simplified, dolphin-adjusted, serum-based MDRD Study equation on 1,103 samples from 50 healthy bottlenose dolphins, we calculated a median predicted GFR of 188 mL/min/2.78 m^2 (range 95–387 mL/min/2.78 m^2), similar to dolphin inulin clearance rates previously reported by Malvin and Rayner in 1968 (mean range of 131–465 mL/min). Further, the dolphin-adjusted MDRD Study equation successfully predicted higher GFR associated with recent feeding. Feeding-associated increases in actual GFR in dolphins have been demonstrated previously by Malvin and Rayner's (1968) inulin clearance studies.

Dietary protein intake of dolphins may explain the significant increase found in actual and predicted GFR when comparing healthy, recently fed dolphins with healthy dolphins not fed overnight. Association between high protein diet intake and increased GFR is well reported in other mammalian species, including humans (Ando et al. 1989). Although the specific cause remains unknown, increases in GFR can be detected in humans and dolphins as early as 1–2 h after eating a high protein meal (Malvin and Rayner 1968, Guyton and Hall 1996).

Seney and Wright (1985) reported that rats fed high protein diets had 24%–29% higher GFR compared to rats fed low protein diets; upon further investigation, the authors hypothesized that high protein diets may suppress the tubuloglomerular feedback system at the single nephron level, leading to increases in GFR. Levine et al. (1986) reported a similar 30% GFR increase in rats provided an oral protein load that was not apparent in rats fed a carbohydrate load. More recently, a study by Yao et al. (2006) suggested that high protein diet-induced increases in GFR were due to nitric oxide mediation of renal cortical cyclooxygenase-2, leading to hyperfiltration, increased proximal sodium chloride reabsorption, and subsequent reduced sodium chloride delivery to the macula densa.

Given the similarity of our predicted GFR findings in postprandial dolphins with studies involving dolphins and other mammals, the serum based, dolphin-adjusted MDRD Study equation may have merit for renal studies involving marine mammal species. Age and sex were significant predictors of GFR in our healthy bottlenose dolphin population. More specifically, predicted GFR was higher in female dolphins compared to male dolphins, and predicted GFR decreased with age. Age-associated GFR decreases in the U.S. adult human population are well documented (Coresh et al. 2003), and mild age-related declines in GFR have been correlated with declines in muscle mass, considered a normal part of aging (Levey 1993).

Although predicted GFR measurements in adult humans may be reliable, the reliability of most GFR prediction formulas for children continues to be questioned; both Pierrat et al. (2003) and Zappitelli et al. (2007) concluded in their studies that none of the commonly applied GFR prediction models for children, including the Schwartz equation, were reliable enough to effectively predict GFR in children. A promising estimator of GFR is the cystatic C prediction equation that can include a prepubertal factor; Grubb et al. (2005) report that this equation provides a better estimation of GFR in children compared to the Schwartz formula as well as in adults compared to the MDRD Study equation. Because the number of data points from fasted dolphins aged <5 yr old were too limited for this study, additional research will need to be conducted to assess the reliability of predicted GFR measurements in young dolphins. In addition, dolphins smaller than 100 kg have a smaller body surface area (Ridgway 1972a), and therefore, our equation would have to be adjusted for this immature population.

Contrary to our findings, lower GFR is reported in women compared to men due to decreased muscle mass and subsequent lower serum creatinine in females compared to males (Swaminathan et al. 1986). Using our same healthy dolphin sample set, we previously reported that male dolphins had significantly higher serum creatinine than female dolphins (Venn-Watson et al., 2007). As such, we expected male dolphins to have a higher predicted GFR compared to female dolphins. The serum-based GFR prediction equation found the opposite result. Follow-on research will need to be conducted to better understand actual sex-associated GFR in dolphins.

We report a 32-yr-old male bottlenose dolphin that died from end-stage renal disease with a correlating decrease in predicted GFR using the dolphin-adjusted

MDRD Study equation. Based upon categories used in human medicine, our case animal had 52 d of declining renal function, including 26 d of severe renal disease that progressed to kidney failure during the last 28 d; this interpretation correlates with clinical observations and diagnostic data, indicating that the dolphin-adjusted MDRD Study equation was able to characterize this dolphin's declining renal function during end-stage renal disease.

Use of a dolphin-adjusted MDRD Study Equation assumes physiological similarities between humans and dolphins. It is known, however, that dolphins have either evolved or exploited mammalian physiological traits that improve survival in the marine environment (Ridgway 1972*b*); adaptations that may affect comparative renal function studies include consistent urine concentration to maximize water conservation and blood shunting around the kidneys for thermoregulation.

Understanding how the human MDRD Study equation has evolved by Levey *et al.* (1999) may provide further insight on the appropriateness of applying a human-based estimated GFR equation to dolphins and may help identify aspects of the equation that need the most adaptation for a different species. Currently, the most widely applied version of the MDRD Study equation for humans is GFR (mL/min/1.73 m^2) = 186 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × (0.742 if female) × (1.180 if black) (Stevens *et al.* 2006). When initially generating the MDRD Study equation, Levey *et al.* (1999) demonstrated that weight and height were not significant predictors of estimated GFR if the average body surface area of an adult human (1.73 m^2) was incorporated into the equation. In our proposed dolphin-adjusted MDRD Study equation, we added a constant multiplier to account for an estimated 1.61 times the average body surface area of an adult dolphin compared to an adult human (2.78 m^2 and 1.73 m^2, respectively). The average dolphin body surface area was calculated using previous measurements acquired on three adult dolphins, but a standardized method of measuring body surface area among a much larger population of dolphins could improve the multiplier used in a dolphin-adjusted MDRD Study equation.

Constant values are included in the human MDRD Study equation to account for known consistent biases, including higher estimated creatinine clearance (*e.g.*, Cockgroft–Gault equation) compared to true GFR. This bias was assumed to be true in dolphins, and the same constants were maintained in the dolphin-adjusted MDRD Study equation. Further studies are needed, however, to confirm that estimated creatinine clearance is consistently higher than actual GFR in dolphins as well as humans.

The human MDRD Study equation uses log-transformed data to correct for increased variability between predicted GFR and true GFR as true GFR increases. Comparisons of estimated and actual GFR in dolphins will need to be conducted to confirm that similar variability occurs with high GFR, thus validating the requirement of log-transformed data for a dolphin-adjusted MDRD Study equation.

When generating the MDRD Study equation, Levey *et al.* (1999) tested several models with potential GFR predictors, including weight; height; age; sex; ethnicity; presence of diabetes; serum creatinine, urea nitrogen, albumin, phosphorus, and calcium; arterial pressure; and urine creatinine, urea nitrogen, protein, and phosphorus levels. Of these, only age, sex, ethnicity, and serum creatinine remained significant predictors of true GFR. Coefficients for each of the final predictors were generated using logistic regression of predictor values against true log GFR, and these coefficients were inserted into the MDRD Study equation (*e.g.*, serum creatinine$^{-1.154}$ and age$^{-0.203}$). Similar refinement of a dolphin-adjusted MDRD Study equation could be conducted using prospective studies measuring true GFR in a series of dolphins.

Actual and predicted GFR are used to categorize stages of chronic kidney disease in humans and to provide guidance for clinical actions (National Kidney Foundation 2002). The five progressing stages of chronic renal disease in humans are defined as follows: Stage 1 = GFR ≤ 90 mL/min (normal or high GFR with kidney damage); Stage 2 = GFR 60–89 mL/min (kidney damage); Stage 3 = GFR 30–59 mL/min (moderate kidney disease); Stage 4 = GFR mL/min 15–29 (severe kidney disease); and Stage 5 = GFR < 15 mL/min (kidney failure). Generation of similar GFR categories in dolphins could be used to guide clinical actions for marine mammal veterinarians with renal disease cases.

Our study is limited due to the retrospective analysis of serum data that were not collected for the primary purpose of our research. Additionally, because our population's dolphins live in open ocean pens, they may eat wild, live fish between fed meals, decreasing the reliability of "fed" vs. "non-fed" blood samples; trainer observations, however, suggest that routine ingestion of wild, live fish is minimal in our dolphin population. Finally, due to inherent limitations with marine mammal research, we were unable to compare predicted GFR with actual GFR by using the gold standard of specific tracer measurements during 24-h urine or serum sample series collections. Although the ability to perform extensive prospective studies involving 24-h total urine collections in dolphins is unlikely, future studies involving well-defined renal cases and controls that are tracked over time will help address how well serum-based GFR equations predict renal disease outcomes in dolphin populations.

In summary, by applying a simplified, dolphin-adjusted MDRD Study equation to predict GFR, we found many parallels between results from our bottlenose dolphin population and those previously reported in humans and other mammals. The effectiveness of a serum-based predicted GFR equation in identifying and tracking early stages of renal disease in dolphins can be further assessed using clearance studies involving 24-h urine or serum series collection in marine mammals.

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