Doppler echocardiographic effects of medetomidine on dynamic left ventricular outflow tract obstruction in cats

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**Objective**—To evaluate the effects of medetomidine on dynamic left ventricular outflow tract (LVOT) obstruction in cats with left ventricular hypertrophy.

**Design**—Clinical trial.

**Animals**—6 domestic shorthair cats with echocardiographic evidence of dynamic LVOT obstruction.

**Procedure**—Cats were restrained in lateral recumbency, and baseline M-mode and Doppler echocardiographic examinations were performed. An ECG was recorded continuously, and blood pressure was measured indirectly with Doppler instrumentation. Medetomidine (20 µg/kg [9.1 µg/lb]) was then administered IM, and examinations were repeated 15 minutes later.

**Results**—Significant decreases in heart rate, LVOT velocity, and the LVOT pressure gradient were documented following medetomidine administration. After adjusting for the effects of heart rate by ANCOVA, there were no significant differences in any other systolic or diastolic indices of left ventricular function.

**Conclusions and Clinical Relevance**—Results suggest that administration of medetomidine to cats with dynamic LVOT obstruction may result in elimination of outflow tract obstruction; medetomidine may be a suitable sedative and analgesic agent in this subpopulation of cats. (J Am Vet Med Assoc 2002;221:1276–1281)

Dynamic left ventricular outflow tract (LVOT) obstruction is a commonly encountered component of hypertrophic cardiomyopathy in cats. At present, hypertrophic cardiomyopathy is considered to be the most common cardiac disease in cats and is believed to have a genetic basis. A phenotypically similar form of left ventricular hypertrophy, also characterized by LVOT obstruction, may develop in cats with hyperthyroidism or, less commonly, systemic hypertension. In human patients with hypertrophic cardiomyopathy, systolic anterior motion of the mitral valve causing mitral septal contact is the usual cause of LVOT obstruction. It has been documented echocardiographically that systolic anterior motion is initiated by flow drag forces acting on the protruding mitral valve leaflet and facilitated by the large angle created with hypertrophy of the ventricle between the leaflet and the jet of left ventricular inflow. Systolic anterior motion of the mitral valve has also been observed in cats with hypertrophic cardiomyopathy and LVOT obstruction and probably operates through the same mechanism.

Left ventricular outflow tract obstruction increases systolic left ventricular pressure, systolic wall tension, and myocardial work. In addition, coronary perfusion pressure is decreased as aortic diastolic pressure decreases and left ventricular diastolic pressure increases. In human patients, these hemodynamic abnormalities may lead to sinus tachycardia associated with hypotension, bradyarrhythmias, ventricular tachyarrhythmias, and myocardial ischemia, which can ultimately cause sudden death. Similarly, sudden cardiac death in cats with idiopathic hypertrophic cardiomyopathy has been reported and is presumably a result of similar types of arrhythmias or ischemia secondary to impaired coronary perfusion.

Many cats with LVOT obstruction do not have any clinically apparent abnormalities and are examined by a veterinarian for a variety of other reasons. In these instances, diagnosis of the underlying cardiac disease may be incidental. Consequently, it is not uncommon for cats with LVOT obstruction to be sedated or anesthetized without prior diagnosis of their condition. However, even if the condition is identified, the particular subpopulation of feline patients represents a unique set of challenges for veterinary anesthesiologists. In human patients, the hemodynamic goals during anesthesia include maintenance of heart rate at low to normal values to facilitate adequate left ventricular filling and ejection, augmentation of systemic vascular resistance to minimize the pressure gradient across the LVOT and reduce obstruction, administration of an adequate volume of a crystalloid or colloid solution to generate high filling pressures, and avoidance of increases in myocardial contractility to decrease left ventricular ejection acceleration.

Unfortunately, most of the commonly used anesthetic agents are not ideal when attempting to achieve these hemodynamic goals in cats with LVOT obstruction. In fact, drugs such as acepromazine, ketamine, and isoflurane may actually make LVOT obstruction worse in the short term. Medetomidine is a synthetic α2-adrenoceptor agonist approved for use as a sedative-analgesic agent in dogs by the FDA. Medetomidine, like other α2-adrenoceptor agonists, possesses a unique spectrum of activity. It consistently induces sedation, analgesia, anxiolysis, and muscle relaxation,
and its effects are completely reversible with the specific antagonist atipamezole. 15

The cardiovascular consequences of medetomidine administration are a result of both altered loading conditions and indirect myocardial depression. First, activation of peripheral $\alpha_2$-adrenoceptors located on postsynaptic membranes in vascular smooth muscle causes vasoconstriction, leading to a transient period of increased systemic vascular resistance and arterial hypertension. 16,20 This, in turn, initiates an arterial baroreceptor response that results in vagally mediated reflex bradycardia. 16,21-23 This combination of increased ventricular afterload and reflex bradycardia profoundly affects cardiac output, with decreases of up to 50 to 66% in cats after medetomidine administration reported. 16

In addition to these peripheral effects, medetomidine has indirect effects on the myocardium itself, through binding to $\alpha_2$-adrenoceptors located centrally in the locus ceruleus. 20,25 Here, presynaptic receptor activation results in inhibition of norepinephrine release from adrenergic nerve terminals, and this decreased sympathetic outflow appears to decrease cardiac output indirectly by depressing the ventricular myocardium in most species. 16 However, medetomidine has not been documented to have any direct effects on myocardial contractility per se.

To our knowledge, the effects of medetomidine on dynamic LVOT obstruction in cats have never been documented. Intuitively, it would seem that the unique cardiovascular alterations induced by this drug may, in fact, help to minimize the pressure gradient generated across the LVOT and thus reduce the degree of obstruction. The purpose of the study reported here was to determine the effects of medetomidine on LVOT obstruction in cats, as determined by means of Doppler echocardiography.

Materials and Methods

Cats—Six privately owned cats (4 male and 2 female) examined by the Cardiology Service of the University of Illinois Veterinary Teaching Hospital were used in the study. All 6 cats fulfilled standard echocardiographic criteria for left ventricular hypertrophy, and all had dynamic LVOT obstruction with pressure gradients $>36$ mm Hg at the time of inclusion in the study. In 4 cats, hyperthyroidism had been diagnosed; in the other 2, no cause for the myocardial hypertrophy was identified, and cats were considered to have idiopathic hypertrophic cardiomyopathy. Cats ranged from 1 to 14 years old and weighed between 2.6 and 6.2 kg (5.7 and 13.6 lb). Mean age was 9 years, and mean weight was 4.9 kg (10.8 lb). Written informed consent was obtained from each owner prior to initiation of the study. The study protocol was approved by the Office of Laboratory Animal Care of the University of Illinois.

Echocardiographic examination—Echocardiographic leads were attached to obtain a standard lead II tracing. Systolic arterial blood pressure was measured indirectly with Doppler instrumentation; the piezoelectric crystal was applied over the dorsal pedal artery, and a neonatal cuff was placed above the tarsus. All echocardiographic measurements were made with a commercially available color-flow mapping system and a 5- or 7.5-MHz transducer. M-mode and 2-dimensional echocardiograms were recorded with cats in right lateral recumbency by imaging the right parasternal window from below through an aperture in a table specifically designed for veterinary echocardiography. Doppler recordings were made from the left side at the cardiac apex, with the cat in left lateral recumbency, by use of both pulsed and continuous wave sample volumes. All indices were obtained with the leading edge method of measurement, as recommended by the American Society of Echocardiography. The complete echocardiographic examination involved measurement and calculation of a variety of values (Appendix).

After the baseline echocardiographic examination was completed, medetomidine (20 $\mu$g/kg [0.1 $\mu$g/lb]) was administered IM. The cats were left undisturbed for 15 minutes, and a second complete echocardiographic examination was performed.

Statistical analyses—Values obtained before and after medetomidine administration were compared by means of 1-way ANOVA for repeated measures. When significant differences were detected, pairwise comparisons were performed with the Tukey test. Effects of heart rate (HR) on isovolumic relaxation time (IVRT) and left ventricular ejection time (LVET) were evaluated with ANCOVA. Values of $P < 0.05$ were considered significant. Data are given as mean $\pm$ SEM.

Results

Echocardiographic examinations before and after medetomidine administration took 30 to 45 minutes to complete. All cats became relaxed and laterally recumbent within 15 minutes after medetomidine administration. Cats were sedate but not entirely unresponsive to stimulation. Two of the cats vomited approximately 5 minutes after IM administration of medetomidine. Recovery from medetomidine was smooth, and none of the cats required reversal with atipamezole. All cats were alert and able to be returned to their owners within 1 hour after medetomidine administration.

Mean HR after medetomidine administration (mean $\pm$ SEM, 123 $\pm$ 9 beats/min) was significantly ($P < 0.001$) decreased, compared with baseline value (214 $\pm$ 11 beats/min), and remained low throughout the second echocardiographic examination. Systolic arterial blood pressure after medetomidine administration (167 $\pm$ 6 mm Hg) was not significantly different from pressure before administration (163 $\pm$ 7 mm Hg), with 4 cats having a slight increase in systolic arterial blood pressure and 2 having a modest decrease. Continuous ECG monitoring indicated that all cats maintained a normal sinus rhythm during both echocardiographic examinations.

Peak LVOT velocity after medetomidine administration (1.1 $\pm$ 0.1 m/s) was significantly ($P < 0.001$) decreased, compared with baseline value (4.7 $\pm$ 0.4 m/s), and was within reference limits (< 1.2 to 1.5 m/s) in all 6 cats after medetomidine injection. Left ventricular outflow tract obstruction and systolic anterior motion of the mitral valve were abolished in all cats after medetomidine administration, and Doppler tracings of LVOT velocity after medetomidine administration indicated a return to a normal flow contour with loss of the characteristic dagger-shaped concavity seen prior to medetomidine injection (Fig 1). The simplified Bernoulli equation was used to estimate the pressure gradient across the LVOT, and the LVOT gradient after medetomidine administration (5.0 $\pm$ 0.7 mm Hg) was significantly ($P = 0.004$) less than the value before medetomidine administration (90.4 $\pm$ 16.6 mm Hg).

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Left ventricular dimensions during systole and diastole did not change after medetomidine administration, with no significant alterations in systolic left ventricular dimension, diastolic left ventricular dimension, systolic left ventricular posterior wall dimension, diastolic left ventricular posterior wall dimension, systolic interventricular septum dimension, or diastolic interventricular septum dimension. The systolic left atrial dimension was significantly (P = 0.017) increased from a mean value of 1.21 cm prior to medetomidine administration to a mean value of 1.29 cm afterward.

Fractional shortening and left ventricular ejection fraction did not change significantly after medetomidine administration; however, circumferential fractional shortening did decrease significantly (P = 0.002) to 79% of the baseline value. Left ventricular ejection time increased significantly (P = 0.025) after treatment; however, after adjustment for the effect of HR on LVET, the change in LVET after medetomidine administration was no longer significant. Left ventricular wall stress did not change significantly after treatment.

Although measured IVRT increased in all 6 cats after administration of medetomidine, an ANCOVA indicated that this change was not significant after the confounding effects of HR on IVRT were considered. Owing to relatively high baseline heart rates, the E and A waves of the transmitral flow velocity profile were fused in 3 of the 6 cats. Consequently, data on E and A waves were available for only 3 cats. Peak E wave velocity did not change significantly after medetomidine administration, but peak A wave velocity decreased significantly (P = 0.048). The E:A wave ratio was not significantly changed after medetomidine administration. Peak E and A wave velocities, normalized to mitral valve stroke volume by dividing by the time-velocity integral of total mitral valve inflow, indicated no change in adjusted E and A wave velocities following medetomidine administration. Maximal E and A wave acceleration and E wave deceleration did not change after medetomidine administration.

**Discussion**

Results of the present study suggest that IM administration of medetomidine (20 µg/kg) may completely eliminate dynamic LVOT obstruction in cats with ventricular hypertrophy. This effect was likely a result of hemodynamic changes arising from increased systemic vascular resistance and decreased HR. Though changes in other echocardiographic indices of left ventricular function were not significantly altered by medetomidine administration, these results may have been confounded to some degree by the effect of medetomidine on cardiac loading conditions. From a clinical perspective, our results indicate that medetomidine may be a suitable sedative-anaesthetic agent for use in this unique subpopulation of cats.

As predicted, administration of medetomidine caused a significant reduction in HR in all 6 cats in the present study. This effect is a vagally mediated response to arterial baroreceptor activation occurring secondary to peripheral vasoconstriction in combination with medetomidine’s general sympatholytic effect. Systolic blood pressure was measured noninvasively in the present study and did not change significantly with medetomidine treatment. Although systemic vascular resistance and cardiac output were not measured in this study, it is likely that medetomidine induced an increase in vascular tone and an accompanying decrease in cardiac output, as has been reported previously in healthy cats. Therefore, the equivocal effects on systolic arterial pressure among cats in the present study were likely a result of increases in systemic vascular resistance coupled with decreases in cardiac output that essentially nullified each other. Continuous monitoring of arterial blood pressure from the time of medetomidine administration may have facilitated recognition of an earlypressor effect; however, there was a concern that any additional stimulation during the first 15 minutes after injection would have had a detectable impact on the level of sedation and anxiolysis achieved.

The most important finding in this study was the complete elimination of dynamic LVOT obstruction and systolic anterior motion of the mitral valve in all 6 cats after medetomidine administration. Maximal LVOT velocities reflect the magnitude of obstruction to outflow and are commonly used to track responses to therapeutic interventions in affected cats. The corresponding pressure gradient across the LVOT can then be estimated with a simplified Bernoulli equation that correlates flow velocity with the accompanying pressure change. In the present study, 1 cat had a baseline LVOT velocity of 6.43 m/s and a pressure gradient of 163.3 mm Hg; these values decreased to 1.24 m/s and 6.2 mm Hg, respectively, after medetomidine injection. This dramatic effect was likely a result of several hemodynamic changes induced by medetomidine. It can be hypothesized that the combination of lowered HR and
increased systemic vascular resistance initiated profound changes in flow dynamics that were key in minimizing the effects of drag forces on the mitral valve apparatus. This would have effectively decreased the chance of mitral-septal contact and establishment of a pressure gradient across the LVOT.\textsuperscript{41} In addition, indirect medetomidine-induced negative inotropic effects associated with general sympatholysis may have played a role in eliminating LVOT obstruction.\textsuperscript{4}

Of the M-mode-derived echocardiographic measurements of left ventricular chamber dimensions, only the systolic left atrial dimension was significantly affected by medetomidine administration in the present study. The observed increase in left atrial size may have been a consequence of impaired left ventricular filling, but more likely was a reflection of increased cardiac afterload imposed by an increase in systemic vascular resistance in combination with marked bradycardia.

The only systolic time interval reported in this study was LVET. Initial analyses indicated that LVET increased significantly after medetomidine administration. However, because this value is extremely sensitive to changes in HR, ANCOVA was used to adjust for the effects of HR on LVET. After this adjustment, values for LVET obtained before and after medetomidine administration were not significantly different. Of the ejection phase indices reported, only circumferential fractional shortening was significantly decreased, compared with baseline values, and this was presumably attributable to the confounding effects of HR on LVET. Fractional shortening and left ventricular ejection fraction were not significantly changed after medetomidine administration, even though these values are sensitive to changes in cardiac loading conditions, particularly afterload.\textsuperscript{26}

The M-mode derived measurements of cardiac chamber dimensions form the foundation for evaluation of ventricular hypertrophy associated with hypertrophic cardiomyopathy and hyperthyroidism in cats. These measurements also are the basis of the commonly cited indices of global cardiac performance, including fractional shortening, left ventricular ejection fraction, and circumferential fractional shortening. Although often considered to be direct assessments of myocardial contractility, all of the ejection phase indices, as well as the systolic time intervals, are extremely sensitive to changes in cardiac loading conditions and, thus, may not truly reflect inherent myocardial function in situations where preload, afterload, or HR have been substantially altered.\textsuperscript{26} For this reason, left ventricular wall stress, which accounts for changes in arterial blood pressure and may be less sensitive to changes in preload and afterload, has been proposed as a potentially superior index of myocardial function.\textsuperscript{26,27} A simplified formula for end-systolic left ventricular wall stress has been proposed; however, this and other similar formulas have not been validated for use in cats. In the present study, the effects of medetomidine on left ventricular wall stress were not consistent. In 4 cats, left ventricular wall stress decreased, and in the other 2, it increased after medetomidine administration. Reasons for this discrepancy are not clear; however, it may suggest that most of medetomidine's effects on cardiovascular performance can be attributed to alterations in cardiac loading conditions and HR, rather than to any direct effects on intrinsic myocardial contractility.

Although assessment of cardiac chamber dimensions and indices of systolic function are common components of clinical echocardiographic examinations in cats, the pathophysiologic changes associated with left ventricular hypertrophy and dynamic LVOT obstruction primarily affect diastolic function. Efforts to adapt echocardiographic indices used to quantitate patterns of ventricular filling and relaxation in human patients for use in veterinary patients are beginning to appear in the literature.\textsuperscript{28,29} Isovolumic relaxation time is considered to be an estimate of the active, or isovolumic, phase of diastole, with longer values for IVRT associated with impaired left ventricular relaxation.\textsuperscript{30,31} In the present study, IVRT was quantified from the 5-chamber view, with the sample volume located midway between the left ventricular inflow and outflow jets. Although prolonged IVRT is associated with impaired left ventricular relaxation, increases in aortic pressure, decreases in left atrial pressure, and decreases in HR can influence measured values without causing true changes in the rate of inherent relaxation.\textsuperscript{28,30} In the present study, initial analyses indicated that IVRT was significantly increased after medetomidine administration; however, after adjustment for the effects of HR with ANCOVA, this difference was no longer significant. Unfortunately, the effects of increased aortic pressure or decreased left atrial pressure on IVRT could not be quantitatively evaluated in this group of cats, so the true impact of medetomidine on the isovolumic phase of diastole in these patients remains uncertain.

Transmitral inflow patterns are also useful tools in evaluating left ventricular diastolic function in human patients, as the rate of left ventricular filling is directly proportional to the mitral flow velocity measured with the Doppler technique.\textsuperscript{32} Typically, Doppler recordings of mitral inflow have a biphasic pattern, with an early peak inflow velocity (E wave) and a late peak inflow velocity (A wave), which corresponds to atrial systole. The ratio of peak E to peak A wave velocities is also commonly reported in human patients, as impaired left ventricular filling is often characterized by a relative decrease in early peak inflow (E wave) and the ratio of E:A ratio < 1.\textsuperscript{31,32} In the present study, mitral inflow was recorded from the 4-chamber view, with the sample volume located at the level of the mitral valve leaflet tips at the point of highest peak flow velocity.

The relatively high baseline HR in these cats made recording of early and late transmitral inflow velocities difficult. Because of E and A wave fusion, we were able to measure distinct E and A wave amplitudes in only 3 of the 6 cats studied. To our knowledge, there are only 2 other published reports\textsuperscript{28,29} of transmitral inflow velocities in cats, and in 1 of these, the cats were anesthetized, thereby permitting easier discrimination of early and late peak filling velocities. All 3 cats in the present study for which data could be obtained had baseline E:A ratios < 1, which is consistent with findings in human patients with hypertrophic cardiomyopathy, in whom the transmitral flow gradient is dimin-
ished because of high left ventricular end-diastolic pressures resulting in less filling during early diastole and a greater reliance on atrial contraction.\(^3\) As is the case with IVRT, transmural inflow patterns are significantly affected by cardiac loading conditions.\(^31,36\) In the present study, the only parameter to significantly change after medetomidine administration was peak A wave velocity, which decreased, compared with baseline values. This was most likely a result of the accompanying reduction in HR.\(^31,37\) Although E and A wave acceleration and E wave deceleration did not change significantly after medetomidine administration, the confounding effects of HR and cardiac loading conditions make it difficult to draw any conclusions regarding medetomidine-induced changes in left ventricular relaxation and compliance.\(^36\)

\(^a\)Ultrasonic Doppler flow detector, model 811, Park Medical Electronics Inc, Dayton, Ohio.


\(^c\)Sigma Stat, Version 2.0, SPSS Science, Chicago, Ill.

\(^d\)Proc GLM, SAS Institute, Cary, NC.


**Appendix**

Variables measured and calculated during a complete echocardiographic evaluation in cats

<table>
<thead>
<tr>
<th>Cardiac chamber measurements</th>
<th>Diastolic left ventricular dimension (LVDd)</th>
<th>Systolic left ventricular dimension (LVDs)</th>
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<tbody>
<tr>
<td>Diastolic left ventricular septum dimension</td>
<td>Systolic left ventricular septum dimension</td>
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<tr>
<td>Diastolic left ventricular posterior wall dimension</td>
<td>Systolic left ventricular posterior wall dimension (LVPWs)</td>
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<tr>
<td>Systolic left atrial dimension</td>
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Indices of global cardiac function

<table>
<thead>
<tr>
<th>Systolic time intervals</th>
<th>Left ventricular ejection time (LVET) = difference between period of electromechanical systole and pre-ejection period</th>
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<tbody>
<tr>
<td>Ejection phase indices</td>
<td>Fractional shortening (FS) = 100 \times \frac{\text{LVDd} - \text{LVDs}}{\text{LVDd}}</td>
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<tr>
<td>Left ventricular ejection fraction = 100 \times \frac{\text{LVEDV} - \text{LVESV}}{\text{LVEDV}}</td>
<td>Circumferential fractional shortening = \frac{\text{FS}}{\text{LVET}}</td>
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<tr>
<td>Myocardial wall stress</td>
<td>Left ventricular wall stress = \frac{\text{FS}}{\text{LVEDV}} \times \text{LVET}</td>
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<tr>
<td>[1 + \frac{\text{LVPWs}^2}{\text{LVDs}^2}]</td>
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Assessment of left ventricular outflow tract (LVOT) flows

<table>
<thead>
<tr>
<th>Peak LVOT velocity (V)</th>
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<tr>
<td>Peak LVOT pressure gradient = 4 \times V</td>
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Assessment of transmural flow

<table>
<thead>
<tr>
<th>Peak E wave (E)</th>
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<tr>
<td>Peak A wave (A)</td>
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<tr>
<td>E/A ratio</td>
</tr>
<tr>
<td>Maximal E wave acceleration</td>
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<tr>
<td>Maximal A wave acceleration</td>
</tr>
<tr>
<td>Maximal E wave deceleration</td>
</tr>
<tr>
<td>Time velocity integral (TVI) of E and A waves</td>
</tr>
<tr>
<td>Normalized peak E wave = \frac{E}{TVI}</td>
</tr>
<tr>
<td>Normalized peak A wave = \frac{A}{TVI}</td>
</tr>
</tbody>
</table>

Assessment of active ventricular relaxation

| Isovolumic relaxation time = time from the end of aortic flow spectral tracing to the onset of mitral valve flow spectral tracing |

\[ \text{LVEDV} = \text{Left ventricular end-diastolic volume}, \text{LVESV} = \text{Left ventricular end-systolic volume}, \text{SAP} = \text{Systolic arterial blood pressure}. \]

**References**


Correction: Predicted ages of dairy calves when colostrum-derived bovine viral diarrhea virus antibodies would no longer offer protection against disease or interfere with vaccination

In the article “Predicted ages of dairy calves when colostrum-derived bovine viral diarrhea virus antibodies would no longer offer protection against disease or interfere with vaccination” (J Am Vet Med Assoc 2002;221:678-685), some of the superscripts used in the text to indicate footnotes were incorrect. The last part of the second paragraph in the “Animals” section on page 679 should read as follows: “For calves from herd B, a killed BVDV vaccine was given at 15 days of age, and a modified-live BVDV vaccine was given at 45 and 180 days of age. Vaccinated calves in the vaccination trial were given a killed BVDV vaccine and leptospira bacterin at 45 days of age, and a modified-live BVDV vaccine at 180 days of age. Control calves in the vaccination trial were given a leptospira bacterin and modified-live virus vaccine without BVDV at 45 days and a modified-live BVDV vaccine at 180 days of age.”

In addition, the footnotes should read as follows:

aOdyssey-3LV+Lepto 5, Agrilabs, St Joseph, Mo.
bElite 4-HS, Bio-Ceutic, St Joseph, Mo.
cExpress 4, Bio-Ceutic, St Joseph, Mo.

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