

## The Influence of a Right-to-left Cardiac Shunt on Lidocaine Pharmacokinetics

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The pharmacokinetics of lidocaine were studied in 1-2-month-old lambs with surgically created, intracardiac right-to-left shunts (RLS) and in age-matched control lambs. Shunts were prepared by anastomosing the pulmonary artery to the left atrial appendage to achieve arterial oxygen saturation of 65-75%. Catheters were implanted both in the right atrium for drug infusion and in the ascending aorta for blood sampling. Lidocaine, 1 mg/kg, injected as a rapid bolus, or 12 mg/kg, injected as a continuous infusion over 15 min, was delivered into the right atrium. Serial samples of arterial blood were obtained every 2.5 s for 1 min following the bolus injection and up to 4 h following the continuous infusion. Samples were analyzed for lidocaine by gas chromatography. Peak arterial whole blood concentration of lidocaine in the shunted animals was  $37.0 \pm 2.1$   $\mu\text{g/ml}$  compared to  $21.1 \pm 0.1$   $\mu\text{g/ml}$  in the control animals;  $P < .01$ . The peak arterial concentrations during the lidocaine infusion were  $12.6 \pm 3.5$   $\mu\text{g/ml}$  in the RLS and  $5.8 \pm 1.5$   $\mu\text{g/ml}$  in the controls. Total body clearance of lidocaine was decreased in the shunted animals to  $30.7 \pm 13.2$   $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  from  $68.1 \pm 12.1$   $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  in the control animals;  $P < .001$ . The steady-state volume of distribution was also decreased in the shunted animals,  $1.0 \pm 0.2$  l/kg versus  $2.0 \pm 0.7$  l/kg in the controls;  $P < .02$ . To induce convulsions  $4.75 \pm 0.46$  mg/kg of lidocaine was required in the shunted animals and  $7.37 \pm 0.44$  mg/kg in the control animals ( $P < .001$ ). Measurements of lidocaine concentrations in blood demonstrated that toxic symptoms occurred at levels which were lower in the shunted animals, but this was not statistically significant. In the presence of an intracardiac RLS, the peak arterial lidocaine concentration was significantly increased after a bolus or continuous infusion of lidocaine, the distribution and clearance of lidocaine were significantly decreased, and there was increased sensitivity to lidocaine neurotoxicity. (Key words: Anesthetics, local; clearance; lidocaine. Heart: congenital heart disease; cyanosis. Pharmacokinetics: lidocaine; right-to-left shunt.)

ALTHOUGH THERE IS considerable information about the pharmacokinetics of amide local anesthetics in

adults, less is known about the pharmacokinetics of local anesthetics in normal infants and children. Surprisingly, the pharmacokinetics of local anesthetics in patients of any age with congenital heart disease (CHD) or in experimental animals with intracardiac shunts, to the best of our knowledge, have never been reported. For example, the recommendations for lidocaine antiarrhythmia therapy in children with CHD are based upon metabolic studies from normal adults.<sup>1</sup>

Under normal conditions, approximately 60-80% of an intravenous lidocaine bolus is absorbed on the first pass through the lungs, then subsequently released over time.<sup>2-6</sup> Patients with CHD and a right-to-left shunt (RLS) have an abnormal circulation. Venous blood returning to the right heart does not pass directly into the lungs because of an obstruction, either complete, such as in pulmonary or tricuspid atresia, or incomplete, such as in tetralogy of Fallot. Under these conditions, much of the venous blood enters directly into the systemic (arterial) circulation through an intracardiac defect, bypassing the lungs.

Our hypothesis is that an anatomical defect causing a RLS could affect lidocaine distribution and elimination. Therefore, the objectives of this study were: 1) to measure the peak arterial concentration of lidocaine following a single intravenous injection, 2) to determine the pharmacokinetics of lidocaine following an infusion, and 3) to identify the convulsive dose of lidocaine in cyanotic animals with surgically created intracardiac RLS.

### Materials and Methods

#### EXPERIMENTAL MODEL

One to two-month-old healthy lambs, approximately 10 kg in weight, were anesthetized with ketamine, 10 mg/kg. Following endotracheal intubation, they were ventilated with an Ohio ventilator regulated at a rate of 15 breaths per minute with halothane, oxygen, and air. Through a left fourth intercostal space thoracotomy, a 4- or 6-mm Gortex® conduit was first sutured to the main pulmonary artery and then connected to the left atrial appendage (fig. 1). Whenever necessary, the size of the shunt was adjusted with sutures to achieve an arterial oxygen saturation varying from 65-75%. After the operation, the lambs were allowed to recover for 2 weeks because of the recognized possibility of decreased

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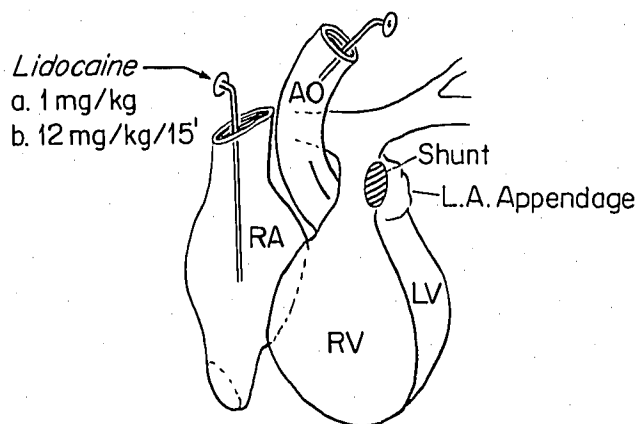


FIG. 1. Right-to-left intracardiac shunt model: connection between main pulmonary artery and left atrial appendage. Catheters are positioned in the right atrium for drug infusion and into the ascending aorta for blood sampling.

hepatic drug clearance in animals as late as 10 days after anesthesia and surgery.<sup>7</sup> Arterial  $P_{aO_2}$  and  $O_2$  saturation was measured using a Corning® 58 blood gas machine and correcting for sheep hemoglobin.<sup>8</sup> Only those lambs with persistent arterial  $O_2$  saturations of 65–75% were selected for further studies. Two to three days before the pharmacokinetic studies, both shunted and age-matched control lambs were anesthetized with ketamine 10 mg/kg im. Heparin-filled polyethylene catheters were placed into the right atrium through the right internal jugular vein and into the ascending aorta via the right carotid artery. The position of the catheters was verified from the pressure tracings and confirmed post-mortem.

#### EXPERIMENTAL PROTOCOL

The awake, unsedated animal was comfortably suspended in a sling for all experiments. Only one study was performed on a lamb in 24 h. Before every experiment, both right atrial and arterial samples were obtained for blood gas analysis and hematocrit determination. The amount of right-to-left shunt,  $Q_p/Q_s$ , was estimated using the equation:

$$\frac{Q_p}{Q_s} = \frac{(ARTO_2 - MVO_2)}{(PVO_2 - PaO_2)},$$

where  $ARTO_2$ ,  $MVO_2$ ,  $PVO_2$  and  $PaO_2$  are systemic arterial, mixed venous, pulmonary venous, and pulmonary arterial blood oxygen saturations, respectively.<sup>9</sup> We assumed  $PVO_2$  saturation was 99% and  $MVO_2$  and  $PaO_2$  saturations were equivalent to right atrial oxygen saturation. We could make these assumptions, since the shunt was placed in the pulmonary artery and there was no mixing between the ventricles. Using this calculation,

$Q_p/Q_s$  in the RLS animals ranged from 0.4–0.6, whereas, for the control animals,  $Q_p/Q_s$  was 0.9.

In the first experiment, an intravenous bolus of lidocaine hydrochloride, 1 mg/kg, was injected within 4 s into the right atrium, and arterial blood samples were collected from the ascending aorta at a rate of 1 sample every 2.5 s for the first minute after the injection, and then at 5, 10, 15, and 30 min. Each sample was analyzed for whole blood concentration of lidocaine as described below.

In the second experiment, 12 mg/kg of lidocaine hydrochloride was infused over 15 min into the right atrium using a constant-rate infusion pump (Harvard Apparatus, South Natick, MA). Arterial blood samples were collected to determine the lidocaine concentration at 5, 10, and 15 min during the infusion, and at 1, 3, 5, 10, 15, 30, 45, 60, 90, 120, 150, and 180 min after the infusion. Lambs were transfused at the end of the study when indicated, or when further pharmacokinetic studies were planned.

In the third experiment, incremental doses of lidocaine hydrochloride, from 4–8 mg/kg, were each injected as a rapid bolus into the right atrium to determine the dose of lidocaine associated with central nervous system (CNS) toxicity. An arterial blood sample was obtained at 60 s after the injection to measure the lidocaine concentration. The dose of lidocaine which induced a convulsion lasting for 90 s or longer was considered neurotoxic. If a convulsion did not occur, the lamb was allowed to recover for 24 h before a higher lidocaine dose was given.

Blood samples were analyzed for whole blood concentration of lidocaine · HCl by gas-liquid chromatography using the method of Mather and Tucker, with mepivacaine as the internal standard.<sup>10</sup> This technique is highly specific and sensitive, measuring as little as 0.05  $\mu$ g of lidocaine per ml of blood. The coefficient of variation of these methods was less than 4% in the range of concentrations measured (0.1–50  $\mu$ g/ml). A Hewlett-Packard® model 5790 gas chromatograph with a Varian model A-25 stripchart recorder was used. The columns were packed with 3% OV-17 (Supelco, Inc., Bellefonte, PA) and held isothermal at 250° C.

Data obtained from the constant infusion studies were analyzed using a two-compartment model with elimination from the central compartment. This model was chosen because it best describes biexponential decay curves of drug concentrations in blood.<sup>11</sup> The best estimates of the pharmacokinetic parameters for volume of distribution and the distribution, elimination, and intercompartmental rate constants were obtained with the nonlinear least-squares program (NONLIN 84®—Statistical Consultants, Lexington, KY). The data were weighted using the reciprocal of the squared

concentrations which permitted a more accurate estimate of the terminal elimination phase. A noncompartmental analysis was conducted to determine the volume of distribution at steady state ( $V_{dss}$ ), clearance ( $Cl$ ), and mean residence time (MRT) using statistical moment theory. Area under the blood concentration · time curve (AUC) and area under the moment curve (AUMC) were estimated by the trapezoidal rule and extrapolated to infinity. Clearance and distribution were determined using the following formulas:

$$Cl = \frac{\text{Dose}}{\text{AUC}} \quad (1)$$

$$V_{dss} = \frac{\text{Dose} \cdot \text{AUMC}}{\text{AUC}^2} - \frac{\text{Dose} \cdot \text{Infusion Time}}{2 \cdot \text{AUC}} \quad (2)$$

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}} \quad (3)$$

The Student's unpaired  $t$  test was used for statistical evaluation of the data.

### Results

In animals with a RLS, peak arterial blood concentrations of lidocaine occurred within 10 s after the injection, whereas peak arterial concentrations occurred within 20 s in the control animals. The peak concentration in the shunted animals averaged  $37.0 \pm 2.1 \mu\text{g/ml}$  compared to  $21.1 \pm 0.1 \mu\text{g/ml}$  in the control animals (fig. 2). After the peak, there was a rapid decline in the blood concentration of lidocaine in all animals over the first minute. During the lidocaine infusion, the peak concentration was  $12.6 \pm 3.5 \mu\text{g/ml}$  at 15 min in the shunted animals compared to  $5.8 \pm 1.5 \mu\text{g/ml}$  at 15 min in the control animals (fig. 3).

From the infusion studies, total body clearance of lidocaine was decreased 55% and the volume of distribution at steady state was 50% smaller in the shunted animals (table 1). Although  $T_{1/2\alpha}$  in the shunted animals was almost twice that of the control animals and  $T_{1/2\beta}$  averaged 25% longer in the shunted animals, these values were not statistically significant.

The dose of lidocaine required to produce convulsions lasting at least 90 s in the shunted animals averaged  $4.75 \pm 0.46 \text{ mg/kg}$  (table 2). In three lambs, the convulsions began within 15 s after the injection, and were associated with an arterial whole blood lidocaine concentration of  $4.9 \pm 2.4 \mu\text{g/ml}$  during the convulsion (1 min after the injection). In the control animals,  $7.37 \pm 0.44 \text{ mg/kg}$  of lidocaine was needed to induce convulsions which began within 30 s after the injection. In three control lambs, the arterial concentration of lidocaine averaged  $11.6 \pm 3.75 \mu\text{g/ml}$  1 min after the injection (statistically not significant from shunted lambs).

PEAK ARTERIAL WHOLE BLOOD LIDOCAINE-HCl (1mg/kg Bolus)

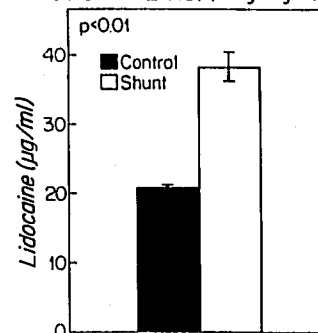


FIG. 2. Peak arterial whole blood lidocaine concentrations ( $\mu\text{g/ml}$ ) following a 1 mg/kg bolus injection into the right atrium. Values are means  $\pm$  SD.

### Discussion

These experiments demonstrate that an intracardiac RLS significantly affects lidocaine pharmacokinetics and pharmacology. The peak arterial concentration of lidocaine doubled, clearance was reduced by more than 50%, and the dose of lidocaine required to produce neurotoxicity was 36% lower in the shunted animals.

Lidocaine, 1–2 mg/kg, is frequently given as an intravenous bolus to treat arrhythmias or before intubation for endotracheal anesthesia to blunt airway reflexes. These studies indicate that in the presence of a RLS, 1 mg/kg of lidocaine given intravenously, resulted in nearly a doubling of the peak arterial blood concentration of the drug as compared to control animals. In the normal circulation, the lungs absorb

LIDOCAINE IN RIGHT TO LEFT CARDIAC SHUNTS

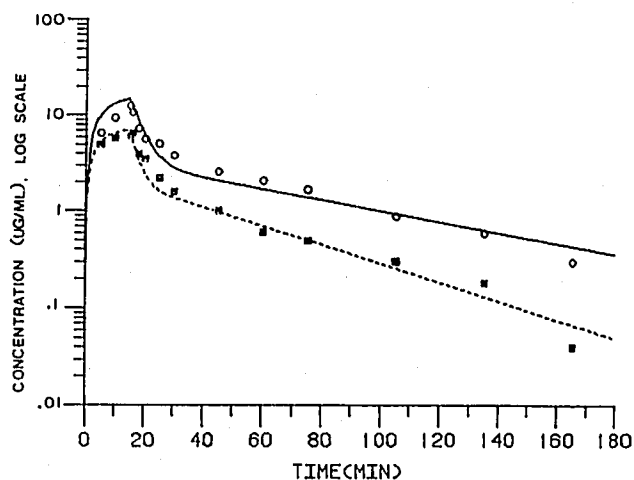


FIG. 3. Log concentration of lidocaine in arterial whole blood following administration of 12 mg/kg over 15 min.  $\circ$  = RLS animals ( $n = 6$ );  $\blacksquare$  = control animals ( $n = 5$ );  $\circ$ ,  $\blacksquare$  = the measured mean concentration of lidocaine at each time. The curves are fitted to the data points.

TABLE 1. Comparison of Lidocaine Pharmacokinetics in Normal and Shunted Lambs Following a 12-mg/kg Infusion into the Right Atrium over 15 Min

	Clearance (ml · kg <sup>-1</sup> · min <sup>-1</sup> )	Vdss (l · kg <sup>-1</sup> )	Vc (l · kg <sup>-1</sup> )	MRT <sup>*</sup> (h)	K10 (min <sup>-1</sup> )	K21 (min <sup>-1</sup> )	K12 (min <sup>-1</sup> )	Cmax (mg · l <sup>-1</sup> )	Alpha t½ (min)	Beta t½ (min)	AUC
Control lambs (n = 5)	68.1 ± 12.1	2.0 ± .7	.5 ± .1	.5 ± .2	.17 ± .1	.04 ± 0.0	.20 ± .2	6.7 ± 1.5	2.3 ± 1.0	37.4 ± 16	143 ± 18
Shunted lambs (n = 6)	30.7 ± 13.2*	1.0 ± .2†	.4 ± .1	.06 ± .03	.08 ± .02	.03 ± .02	.11 ± .1	10.9 ± 3.8	4.4 ± 4.3	51.6 ± 22	496 ± 85*

Values given are means ± SD. Vdss = volume of distribution at steady state; Vc = volume of central compartment; MRT = mean residence time; AUC = area under time · concentration curve.

\*  $P < .001$ , comparing RLS vs. control animals.

†  $P < .02$ , comparing RLS vs. control animals.

60–80% of a lidocaine bolus on its first passage.<sup>2–6</sup> In the presence of a RLS, a portion of the venous blood entering the right side of the heart passes directly into the systemic circulation, bypassing the lungs. Consequently, the lungs cannot protect against potentially toxic arterial concentrations. Besides possible neurotoxic effects, these findings are of additional concern because significant myocardial toxicity has been demonstrated at arterial blood lidocaine concentrations of 27.6 µg/ml in adult sheep and 35.6 µg/ml in neonatal lambs.<sup>12</sup> In lambs with a RLS, the peak arterial blood lidocaine concentration from only 1 mg/kg of lidocaine measured 37.0 µg/ml. However, this transient elevation followed by a rapid decline did not cause any recognizable CNS or cardiovascular toxicity.

Morishima *et al.* found lidocaine clearance in neonatal lambs to be 53.5 ml · min<sup>-1</sup> · kg<sup>-1</sup>, which is comparable to our results in 1–2-month-old control lambs of 68.1 ml · min<sup>-1</sup> · kg<sup>-1</sup>.<sup>13</sup> However, in shunted animals, the total body clearance of lidocaine was considerably reduced. Normally, less than 1–5% of lidocaine is excreted unchanged by the kidneys.<sup>13–14</sup> Thus, lidocaine elimination occurs primarily as a result of hepatic metabolism.<sup>15</sup> The major factors which determine hepatic clearance ( $Cl_h$ ) are hepatic blood flow ( $Q_h$ ), free fraction or unbound drug in the blood ( $f_b$ ), and the metabolic

capacity of the liver enzymes ( $Cl'$ ). This relationship has been described mathematically as:<sup>16</sup>

$$Cl_h = Q_h \left( \frac{f_b \cdot Cl'}{Q_h + f_b Cl'} \right)$$

If any of the above terms are decreased, the result will be a decrease in apparent hepatic clearance. The hepatic extraction ratio of lidocaine is very high (>0.9) in adult sheep.<sup>17</sup> Since the liver has such a great capacity to metabolize lidocaine, all or most of the drug in the blood, whether bound or unbound, is removed as it passes through the liver. Consequently, the  $Cl_h$  of lidocaine is considered to be primarily hepatic blood flow dependent, and should be little affected by moderate changes in the activity of drug metabolizing enzymes or by changes in drug binding to blood proteins.<sup>7,18</sup> Consequently, the significant decrease in clearance of lidocaine in the presence of a RLS should be most likely due to decreased hepatic blood flow. To the best of our knowledge, there are no reported studies on liver blood flow in animals or humans with chronic RLS or chronic cyanosis.

Though apparent hepatic clearance may be a relatively insensitive measure, hepatic oxidative enzyme activity could also be decreased as a result of chronic cyanosis. Benowitz *et al.* found in cyanotic animals in cardiogenic shock that the decrease in lidocaine clearance did not correlate with the anticipated decrease in hepatic blood flow.<sup>19</sup> In another study by Moore *et al.*, halothane metabolites in children with cyanotic CHD derived primarily from the reductive pathways, whereas, in noncyanotic children, oxidative metabolites predominated.<sup>20</sup> We are currently conducting experiments to determine the relative importance of hepatic blood flow, oxidative enzyme function, and protein binding of lidocaine in chronic RLS.

The volume of distribution of lidocaine is affected primarily by changes in blood and tissue binding according to the following equation:

TABLE 2. Mean Dose (±SEM) of Lidocaine Necessary to Produce Convulsions and Mean Arterial Concentration (±SEM) of Lidocaine 1 Min after Injection during the Convulsion

	Lidocaine Dose mg/kg	Lidocaine Concentration µg/ml
Control lambs	7.37 ± 0.16 (n = 8)	11.6 ± 2.2 (n = 3)
Shunted lambs	4.75 ± 0.18* (n = 7)	4.9 ± 1.4† (n = 3)

\*  $P < .001$ , comparing RLS vs. control animals.

† Not statistically significant,  $P < .06$ .

$$V_d = V_B + V_T \frac{f_b}{f_T},$$

where  $V_d$  is the volume of distribution,  $V_B$  is the volume of the blood compartment,  $V_T$  is the volume of the tissue compartment,  $f_b$  is the free fraction (unbound) of lidocaine in the blood, and  $f_T$  is free fraction of lidocaine in the tissue. Either an increase in blood protein binding or decreased tissue binding of lidocaine will decrease the  $V_d$ .

In the blood, lidocaine binds primarily to  $\alpha_1$ -acid glycoprotein which has been reported to increase substantially following trauma, surgery, and severe stress.<sup>7</sup> Although we did not measure  $\alpha_1$ -acid glycoprotein in this study, it is possible that the shunted animals had increased production of this protein as a result of the surgery or from the stress of chronic cyanosis. Whereas increased protein binding has little effect on the clearance of lidocaine, it will decrease the volume of distribution of lidocaine.<sup>7,18</sup> In addition, considering that the lung is a major source of tissue uptake for lidocaine, by totally or partially eliminating the lungs from the circulation in a RLS, the volume of distribution should be decreased.<sup>†</sup> Both of these factors, decreased free fraction of lidocaine in the blood (from increased protein binding) and decreased lung uptake of lidocaine (increased  $f_T$ ) could account for the diminished volume of distribution observed in the shunted animals.

Alternatively, all previously published reports on the role of the lungs in lidocaine pharmacokinetics consider the lung to be important in lidocaine distribution but not elimination. The consensus is that lidocaine is absorbed but not metabolized by the lungs.<sup>15,17</sup> Nevertheless, Mather *et al.* found in two sheep that the mean total body clearance of lidocaine was considerably greater than the sum of renal and hepatic clearances, suggesting that organs or regions other than the kidneys or the liver contributed to lidocaine clearance.<sup>17</sup> Our data suggest that the lungs could be involved in lidocaine elimination, but further experiments are needed to confirm this theory.

Morishima *et al.* reported that  $5.8 \pm 1.8$  mg/kg of lidocaine when given as a continuous infusion induced convulsions in adult sheep, while the neurotoxic dose in 1–5-day-old lambs was  $18.4 \pm 2.2$  mg/kg.<sup>12</sup> The con-

trol lambs in this study convulsed with  $7.37 \pm 0.44$  mg/kg lidocaine when given as a bolus injection. One would anticipate that 1–2-month-old lambs would convulse at a lower dose of lidocaine than neonatal animals. Interestingly, the lambs with a RLS convulsed at a dose of lidocaine 36% lower than the control lambs (table 2). Furthermore, it appears that the convulsive threshold may be lower in animals with a RLS, since the arterial concentration of lidocaine during the convulsion was only  $4.9 \pm 2.4$   $\mu$ g/ml as compared to  $11.6 \pm 3.75$   $\mu$ g/ml in the control lambs. Morishima measured the concentration of lidocaine at  $11.7 \pm 2.0$   $\mu$ g/ml in adult sheep at the onset of convulsions, and at  $16.6 \pm 1.2$   $\mu$ g/ml in newborn lambs.<sup>13</sup> Since, in animals with a RLS, the lungs are partially bypassed, we anticipated that a lower dose of intravascularly injected lidocaine would be necessary to induce convulsions because a higher concentration of the drug would reach the systemic circulation and, hence, the CNS. The lower arterial concentration of lidocaine measured in the shunted animals during the convulsion implies that chronic cyanosis may also enhance neurotoxicity by local anesthetics. However, these data are too limited ( $n = 3$ ) to draw such a conclusion at this time.

In conclusion, we have demonstrated in animals with an intracardiac RLS that 1 mg/kg of lidocaine given as an intravenous bolus directly into the right atrium is associated with significantly higher and potentially toxic arterial blood concentrations; that the distribution and clearance of lidocaine following an infusion is significantly decreased; and that the neurotoxic threshold dose of lidocaine is lower. Extrapolation of these experimental findings in lambs to humans is fraught with the usual limitations. In addition, we recognize that, in many clinical situations, lidocaine is slowly infused into a peripheral vein rather than given as a rapid bolus into the right atrium, thereby significantly diluting the drug. We, nevertheless, selected the right atrial injection in order to maximize the effects of a bolus lidocaine injection in the presence of a RLS. Furthermore, clinical parallels of this situation do occur, for example, in patients with a RLS (*i.e.*, tetralogy of Fallot, transposition of the great vessels, tricuspid or pulmonary atresia) having surgery in whom a right atrial catheter would be placed pre-induction for volume assessment and drug administration. Under these circumstances, the dose of lidocaine should be reduced and the drug should be delivered very slowly. Finally, the result we want to emphasize is the 50% decrease in clearance of lidocaine in chronic RLS. At this time, it is unknown whether this is a result of altered liver blood flow or decreased oxidative enzyme function. It is also likely that other drugs with high intrinsic clearance by the liver, such as ketamine, verapamil, propranolol, and meperidine, would

<sup>†</sup> Lidocaine binding in tissues is probably different for each tissue type. Since the lung is a major contributor to lidocaine uptake, a more applicable equation would be:  $V_d = V_B + (V_{Lung} \cdot f_b/f_{Lung}) + (V_T \cdot f_b/f_T)$ , where  $V_{Lung}$  is the volume of the lung and  $f_{Lung}$  is the free fraction (unbound) lidocaine in the lung.  $V_T$  and  $f_T$  are the volume and free fraction of all other tissues. Consequently, by totally or partially eliminating the lungs from the circulation, the total volume of distribution will decrease.

also have decreased clearance in the presence of a chronic RLS.

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