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Cardiovascular and Electrophysiologic Interactions between Diltiazem and Isoflurane in the Dog

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The effects of the calcium entry blocker diltiazem (iv loading dose 0.4 mg/kg, iv maintenance dose 0.4 mg/min) and subsequent isoflurane-induced hypotension to mean aortic pressures of 70 and 55 mmHg on global and regional right ventricular (RV) and left ventricular (LV) performance (ultrasonic dimension technique), on coronary (electromagnetic flow probes) and systemic hemodynamics, and on electrophysiologic parameters (PR, QRS, QT_c intervals) were studied in eight open-chest dogs, anesthetized and paralyzed by continuous infusions of fentanyl and pancuronium. Diltiazem at a plasma concentration of 282 ± 33 ng/ml (mean ± SE) caused significant ($P < 0.05$) increases in coronary blood flows, and decreases in coronary and systemic vascular resistances with only little effect on global and regional RV and LV function. However, the PR interval increased by 40%, and three animals developed II° atrioventricular block type I. At stable diltiazem plasma levels, administration of isoflurane caused dose-dependent decreases in myocardial segment shortening and stroke volume with unchanged LV or increased RV preload, and little changed RV or reduced LV afterload indicating myocardial depression. Coronary and systemic vascular resistances remained unaffected. At the higher concentration of isoflurane (mean inspired 1.3 ± 0.2%), seven animals developed intermittent sinus node arrests with pauses up to 12 s followed by intermittent junctional escape or sinus rhythms. Similar interactions might develop in patients on diltiazem receiving isoflurane. (Key words: Anesthetics, volatile: isoflurane. Heart: coronary hemodynamics; regional myocardial performance. Pharmacology: diltiazem.)

WHEREAS ALL CALCIUM ENTRY BLOCKERS inhibit Ca^{2+} influx activated by membrane depolarization as well as α-adrenergic receptor stimulation,[1,2] each of the commonly used calcium entry blockers—diltiazem, verapamil and nifedipine—possesses distinct cardiovascular and electrophysiologic profiles.[3–5] The latter also applies to inhalational anesthetics.[6,7] It is, therefore, important to define the specific interaction between individual calcium entry blockers and individual volatile anesthetics.

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Diltiazem is used effectively in the treatment of coronary vasospasm[8] and angina pectoris.[9] It has several characteristics in common with isoflurane; although at somewhat different sites they both interfere with calcium ion flux,[2,10,11] and cause dose-dependent myocardial depression,[3,12,13] systemic and coronary vasodilation,[13–17] and depression of sinus node function.[18,19] Thus, significant cardiovascular as well as electrophysiologic interactions are to be expected. Such interactions have been reported *in vivo*[20] and *in vitro*.[21]

This study was designed (a) to define the effects of diltiazem at clinically relevant plasma levels on right and left ventricular global and regional myocardial performance, on coronary hemodynamics, and on electrophysiologic parameters, and (b) to characterize cardiovascular and electrophysiologic interactions between diltiazem and isoflurane at two levels of isoflurane-induced hypotension.

Materials and Methods

INSTRUMENTATION

Eight mongrel dogs of either sex weighing between 27 and 33 kg were premedicated with intramuscular fentanyl (0.04 mg/kg) and droperidol (2 mg/kg), anesthetized and paralyzed with continuous iv infusions of pentobarbital (1 $mg \cdot kg^{-1} \cdot h^{-1}$), fentanyl (20 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and pancuronium (0.04 $mg \cdot kg^{-1} \cdot h^{-1}$), and ventilated as previously described.[13] Sodium bicarbonate was administered if the calculated base deficit exceeded 5 mEq/L. All dogs were in the supine position and placed on a heating element incorporated in the operating table. Body temperature was continuously monitored by a thermistor of a flow-directed thermodilution catheter (Edwards Laboratory, Santa Ana, CA, Model 93-132-5F) positioned in the pulmonary artery. All animals received 4–6 $ml \cdot kg^{-1} \cdot h^{-1}$ of normal saline.

Catheter-tip manometers (6F, Millar Instruments Inc, Houston, TX) were advanced into the ascending aorta just above the aortic valve, and into the left (LV) and the right ventricles (RV), and calibrated as previously described.[13] The chest was entered through a median sternotomy, and the heart was suspended in a pericardial cradle. Precalibrated electromagnetic flow probes (Stölzer Messtechnik, Waldkirch, West Germany) of appropriate sizes to ensure a snug fit were placed around the ascending aorta, the right coronary artery (RCA) approximately 1–2 cm distal to its origin, and the left anterior descending

coronary artery (LAD) distal to its first large diagonal branch. The flow probes were connected to flow meters with incorporated nonocclusive zero (Hellige Co., Freiburg i. Br., West Germany).

Regional Myocardial Function

Regional myocardial performance was evaluated by sonomicrometry.[22,23] Pairs of piezoelectric crystals (5 MHz, 1.5–2.0 mm diameter) were inserted into the subendocardium of the inflow (longitudinal direction) and outflow tract (transverse direction) of the RV. A third pair was inserted in an equatorial plane into the subendocardium of the LV distal to the first or second diagonal branch of the LAD. Care was taken to place the crystals in the inflow tract of the RV and those in the apical region of the LV within the areas supplied by the RCA and LAD, respectively. Myocardial segment lengths (SL) between each pair of crystals were determined at end diastole (SL_{ed}) and at the time of maximal shortening during systole (SL_{sys}). From these values, per cent segment shortening during systole (ΔSL) was derived [ΔSL (%) = $(SL_{ed} - SL_{sys})/SL_{ed} \cdot 100$]. End diastole was defined as the beginning of the sharp upslope in the expanded LV and RV pressure tracings, and end systole by the dicrotic notch in the aortic pressure signal as derived from the catheter-tip manometers. The ultrasonic signals were also assessed visually for qualitative changes such as akinesis, paradoxical systolic segment lengthening, or postsystolic segment shortening.[24]

Hemodynamic Measurements

A multichannel recorder (Hellige Co., Freiburg i. Br., West Germany) was used for the continuous recording of all signals. LV maximum rate of tension development (dP/dt) was derived from LV high-fidelity signals using operational amplifiers connected to a differentiator (Hellige Co., Freiburg i. Br., West Germany). Systemic (SVR), pulmonary (PVR), and right (CVR_{RCA}) and left anterior descending (CVR_{LAD}) coronary artery vascular resistances, right (RVSW) and left ventricular stroke work (LVSW), and stroke volume (SV) were derived from standard formulae.[13]

Electrocardiographic (ECG) Measurements

The ECG was recorded at a chart speed of 100 mm/s, and at least five cardiac cycles were analyzed for rate (R-R intervals) and rhythm, PR intervals, and QRS and QT duration. The latter was corrected for heart rate (QT_c). In the case of second degree (II°) atrioventricular (AV) block type I (Wenckebach phenomenon), the mean duration of the successively lengthening PR intervals was recorded. In the case of sinus node arrests or AV junctional rhythm followed by intermittent sinus rhythm (SR), rate and intervals of the intermittent SR were recorded.

Experimental Protocol

After the sternotomy and approximately 2 h prior to the start of the experiment, pentobarbital was discontinued. Any adjustments in ventilation, acid-base status, depth of anesthesia, and fluid administration were made no later than 30 min prior to the start of the experiment. At the end of the surgical preparation, at least 30 min were allowed for stabilization. With the introduction of isoflurane, the rate of fentanyl infusion was reduced by approximately 30% to 15 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Arterial blood samples were taken at the end of each experimental period for determination of hematocrit (Hct; Microcentrifuge Compur, Munich, Model M1100), arterial blood gases and arterial *p*H (Instrumentation Laboratory, Lexington, MA, Model 613), and diltiazem plasma levels. Diltiazem was assayed by electron-capture gas-liquid chromatography.[25] As internal standard, the butyryl analogue of diltiazem was used. This method has an overall sensitivity of less than 5 ng/ml of plasma.

Hydrophilized diltiazem hydrochloride dissolved in distilled water was freshly added to 0.9% NaCl to yield concentrations of 1 mg/ml and 0.4 mg/ml for bolus injection and continuous infusion, respectively. After control readings (C) had been obtained, an iv loading dose of diltiazem (0.4 mg/kg) administered as two bolus doses (0.2 mg/kg each) was followed by a continuous infusion (0.4 mg/min), which was maintained throughout the remainder of the experiment. Approximately 20 min after the start of the infusion, repeat measurements during steady-state conditions of diltiazem infusion were made (D), and isoflurane was subsequently administered through a precalibrated vaporizer at concentrations to reduce AoP_m first to 70 mmHg (D+ISO1), and subsequently to 55 mmHg (D+ISO2). Blood samples and measurements were taken after hemodynamic stabilization which occurred approximately 25 min after introduction of each of the two isoflurane concentrations. All measurements were made at end expiration.

Statistical Analysis

The data were statistically analyzed by Friedman's statistic. If this indicated statistical significance, the Wilcoxon signed-rank test was used to isolate the significant difference between treatments by making pairwise comparisons.[26] A P value of <0.05 was considered statistically significant.

Results

Diltiazem plasma levels (means ± SE) during D, D+ISO1, and D+ISO2 were 282 ± 33 ng/ml (206–459), 293 ± 36 ng/ml (213–494), and 333 ± 41 ng/ml (157–520), respectively (Table 1). There were no statistically significant differences among them. Changes in pH_a,

TABLE 1. Diltiazem Plasma Levels and Measures of General Homeostasis

Variable	C	D	D+ISO1	D+ISO2
Diltiazem (ng/ml)	—	282 ± 33	293 ± 36	333 ± 41
pHa	7.37 ± 0.01	7.36 ± 0.01	7.37 ± 0.01	7.38 ± 0.01
PaO_2 (mmHg)	248 ± 15	237 ± 20	279 ± 14	261 ± 9
$PaCO_2$ (mmHg)	38 ± 1	36 ± 1	36 ± 1	34 ± 1*†
Hct (%)	35 ± 1	37 ± 1	36 ± 1	35 ± 1
T (C°)	37.6 ± 0.2	37.6 ± 0.1	37.5 ± 0.2	37.4 ± 0.1

Values are means + SE. C = control. D = diltiazem. D+ISO1 and D+ISO2 = concentrations of isoflurane (ISO) during continuous infusion of D that reduced mean aortic pressure to 70 mmHg (D+ISO1) and 55 mmHg (D+ISO2), respectively.
* = $P < 0.05$ compared to C.
† = $P < 0.05$ compared to D.

Pa_{CO_2}, Hct, and temperature were among minimal throughout the experiment (table 1).

Effects of Diltiazem on Systemic Hemodynamics and LV Function

There was a small (approximately 5%) but significant fall in mean aortic pressure (AoP_m), a decrease in SVR, and an increase in aortic flow (AoF). All other parameters remained unaffected (table 2).

Effects of Diltiazem on Pulmonary Hemodynamics and RV Function

As in the LV, per cent segment shortening during systole (ΔRVITSL, ΔRVOTSL) did not change. In contrast to the LV, end diastolic (SL_{ed}) as well as systolic segment lengths (SL_{sys}) in the RV inflow (RVIT) and outflow tract (RVOT) increased. In contrast also to the effects on the systemic circulation mean pulmonary artery pressure (PAP_m) and pulmonary vascular resistance (PVR) remained unchanged (table 3).

Effects of Diltiazem on Coronary Hemodynamics

There were pronounced increases in CBF_{LAD} and CBF_{RCA} by approximately 40 and 60%, respectively, with similar increases in coronary blood flow (CBF) as a fraction of AoF (CBF/AoF), and decreases in CVR_{LAD} and CVR_{RCA}.

Effects of Diltiazem on Cardiac Rhythm and Electrophysiologic Parameters

PR intervals increased by 40% while QRS intervals and QT_c duration remained unaffected. Three animals developed persistent II° AV block type I (Wenckebach phenomenon) with conductions varying between 4:3, 5:4, 6:5, and 9:8, and with PR intervals varying from 0.18–0.28 (table 5).

Effects of Addition of Isoflurane on Systemic Hemodynamics and LV Function

It required mean inspired concentrations of 0.8% ± 0.1 (range 0.5–1.3%) and 1.3% ± 0.2 (range 0.7–2.1%) to lower AoP_m to 70 mmHg (D+ISO1) and 55 mmHg (D+ISO2), respectively. Isoflurane caused dose-dependent decreases in LV dP/dt, LVSW, LV segment length shortening (ΔLVSL), AoF, and SV, and an increase in LV systolic segment lengths. LV end diastolic pressure and LV end diastolic segment lengths ($LVSL_{ed}$) did not change significantly. Qualitative changes in sonomicrometry signals, such as akinesis, paradoxical systolic segment lengthening, or postsystolic shortening, were not seen. Heart rate (HR) and systemic vascular resistance (SVR) remained unchanged (table 2).

TABLE 2. Effects of Diltiazem and Subsequent Isoflurane-induced Hypotension on Systemic Hemodynamics and Left Ventricular Function

Variable	C	D	D+ISO1	D+ISO2
AoP_m (mmHg)	94 ± 3	89 ± 3*	70 ± 1*†	55 ± 2*†‡
LV dP/dt_{max} (mmHg/s)	2492 ± 163	2522 ± 192	1942 ± 153*†	1333 ± 88*†‡
LVEDP (mmHg)	5.9 ± 0.4	6.3 ± 0.6	5.8 ± 0.6	6.4 ± 0.7
LVSW (g·m)	26.9 ± 2.8	27.5 ± 3.2	17.7 ± 1.6*†	11.3 ± 1.6*†‡
$LVSL_{ed}$ (mm)	9.2 ± 0.4	9.3 ± 0.2	9.1 ± 0.3	9.9 ± 0.5
$LVSL_{sys}$ (mm)	6.3 ± 0.3	6.4 ± 0.2	6.6 ± 0.3*	7.7 ± 0.5*†‡
ΔLVSL (%)	31.2 ± 3.2	31.7 ± 3.1	27.9 ± 2.9†	22.6 ± 2.4*†‡
AoF (l/min)	2.0 ± 0.2	2.4 ± 0.3*	1.9 ± 0.2†	1.4 ± 0.2*†‡
HR (beats/min)	94 ± 6	99 ± 8	95 ± 6	82 ± 5
SV (ml/beat)	22 ± 2	24 ± 2	20 ± 2†	17 ± 2*†‡
SVR ($dyn \cdot s \cdot cm^{-5}$)	3649 ± 177	3151 ± 321*	2940 ± 288*	3182 ± 318

Values are means ± SE.
AoP_m = mean aortic pressure. LVEDP = left ventricular (LV) end diastolic pressure. LVSW = LV stroke work. $LVSL_{ed}$ = LV end diastolic segment length. $LVSL_{sys}$ = LV systolic segment length. ΔLVSL = LV segment shortening. AoF = aortic flow. HR = heart rate. SV = stroke volume. SVR = systemic vascular resistance.
* = $P < 0.05$ compared to C.
† = $P < 0.05$ compared to D.
‡ = $P < 0.05$ compared to D+ISO1. (See Table 1 for further abbreviations.)

TABLE 3. Effects of Diltiazem and Subsequent Isoflurane-induced Hypotension on Pulmonary Hemodynamics and Right Ventricular Function

Variable	C	D	D+ISO1	D+ISO2
PAP_m (mmHg)	13 ± 1	14 ± 1	13 ± 1	12 ± 1†
RVSP (mmHg)	29 ± 2	30 ± 1	27 ± 1†	25 ± 1*†‡
RVSW (g · m)	2.9 ± 0.6	3.4 ± 0.5	2.5 ± 0.5†	1.8 ± 0.5*†‡
RVEDP (mmHg)	3.6 ± 0.3	3.9 ± 0.3	3.9 ± 0.3	4.6 ± 0.5
$RVITSL_{ed}$ (mm)	10.3 ± 0.6	10.7 ± 0.6*	10.6 ± 0.7*	10.8 ± 0.7*
$RVITSL_{sys}$ (mm)	8.1 ± 0.6	8.4 ± 0.6*	8.6 ± 0.6*	9.2 ± 0.7*†‡
ΔRVITSL (%)	22.0 ± 1.4	21.7 ± 1.8	19.8 ± 1.7	15.6 ± 2.1*†‡
$RVOTSL_{ed}$ (mm)	10.5 ± 0.8	11.3 ± 0.8*	11.5 ± 0.9*	12.1 ± 1.1*†‡
$RVOTSL_{sys}$ (mm)	8.0 ± 0.7	8.5 ± 0.6*	8.9 ± 0.7*†	10.2 ± 0.9*†‡
ΔRVOTSL (%)	24.1 ± 1.7	24.5 ± 0.7	22.4 ± 1.0†	16.3 ± 1.1*†‡
PVR ($dyn \cdot s \cdot cm^{-5}$)	274 ± 31	290 ± 35	299 ± 31	358 ± 58

Values are means ± SE.

PAP_m = mean pulmonary artery pressure. RVSP = right ventricular (RV) systolic pressure. RVSW = RV stroke work. RVEDP = RV end diastolic pressure. $RVITSL_{ed}$ = RV inflow tract (RVIT) end diastolic segment length. $RVITSL_{sys}$ = RVIT systolic segment length. ΔRVITSL = RVIT segment shortening. $RVOTSL_{ed}$ = RV outflow tract (RVOT) end diastolic segment length. $RVOTSL_{sys}$ = RVOT systolic segment length. ΔRVOTSL = RVOT segment shortening. PVR = pulmonary vascular resistance.

* = $P < 0.05$ compared to C.

† = $P < 0.05$ compared to D.

‡ = $P < 0.05$ compared to D+ISO1. (See Table 1 for further abbreviations.)

Effects of Addition of Isoflurane on Pulmonary Hemodynamics and RV Function

There were dose-dependent decreases in PAP_m, RV systolic pressure (RVSP), and RVSW. Changes in RV outflow tract (RVOT) and RV inflow tract (RVIT) were quantitatively different, but qualitatively similar. ΔRVOTSL decreased in a dose-dependent fashion, whereas ΔRVITSL decreased significantly only during D+ISO2. In the RVOT, SL_{ed} was significantly elevated during D+ISO2, and SL_{sys} increased in a dose-dependent fashion. In contrast, in the RVIT, SL_{ed} did not increase significantly, and SL_{sys} was significantly elevated only during D+ISO2. As in the LV, there were no qualitative changes in the sonomicrometry signals (table 3).

Effects of Addition of Isoflurane on Coronary Hemodynamics

CBF_{LAD} and CBF_{RCA} decreased by approximately 20% and 45% during D+ISO1 and D+ISO2, respectively. CVR_{LAD} and CVR_{RCA}, as well as CBF/AoF, remained unchanged (table 4).

Effects of Addition of Isoflurane on Cardiac Rhythm and Electrophysiologic Parameters

PR and QRS intervals, and QTc duration, did not change significantly. During D+ISO1, those three animals that had developed II° AV block type I continued to have this type of block with a tendency for shorter Wenckebach periods. In another two animals, intermittent sinus node arrests developed with pauses of approximately 2.5 s, followed by intermittent junctional escape rhythms or intermittent SR.

During D+ISO2, seven of the eight animals developed intermittent sinus node arrests, and one animal continued to have II° AV block type I. The pauses following the sinus node arrests ranged from 1.1–12.2 s (mean 4.8 s). The rates of the intermittent junctional escape rhythms varied between 24 and 66 beats/min (mean 44 beats/

TABLE 4. Effects of Diltiazem and Subsequent Isoflurane-induced Hypotension on Left and Right Coronary Hemodynamics

Variable	C	D	D+ISO1	D+ISO2
CBF_{LAD} (ml/min)	27 ± 3	37 ± 5*	29 ± 4†	20 ± 3*†‡
CBF_{RCA} (ml/min)	14 ± 1	22 ± 3*	17 ± 2†	12 ± 1†‡
CVR_{LAD} ($Kdyn \cdot s \cdot cm^{-5}$)	241 ± 23	174 ± 26*	167 ± 24*	179 ± 25*
CVR_{RCA} ($Kdyn \cdot s \cdot cm^{-5}$)	530 ± 40	363 ± 55*	338 ± 42*	362 ± 36*
CBF_{LAD}/AoF · 100 (%)	1.32 ± 0.13	1.63 ± 0.19*	1.57 ± 0.22	1.53 ± 0.18
CBF_{RCA}/AoF · 100 (%)	0.72 ± 0.06	0.95 ± 0.10*	0.93 ± 0.11	0.92 ± 0.13

Values are means ± SE.

CBF_{LAD} = mean left anterior descending coronary artery blood flow. CBF_{RCA} = mean right coronary artery blood flow. CVR_{LAD} = left anterior descending coronary artery vascular resistance. CVR_{RCA} = right coronary artery vascular resistance.

* = $P < 0.05$ compared to C.

† = $P < 0.05$ compared to D.

‡ = $P < 0.05$ compared to D+ISO1. (See Table 1 for further abbreviations.)

TABLE 5. Effects of Diltiazem and Subsequent Isoflurane-induced Hypotension on Electrocardiographic Intervals

Interval	C	D	D+ISO1	D+ISO2
PR (s)	0.14 ± 0.01	0.20 ± 0.01*	0.21 ± 0.01*	0.21 ± 0.01*
QRS (s)	0.08 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	0.08 ± 0.01
QT_c (s)	0.33 ± 0.01	0.33 ± 0.01	0.36 ± 0.01	0.35 ± 0.02

Values are means ± SE.

* = $P < 0.05$ compared to C. (See Table 1 and text for further abbreviations.)

min), and the rates of the intermittent SR varied between 71 and 101 beats/min (mean 88 beats/min). There was no slowing of heart rate prior to loss of the P wave.

In five animals with intermittent sinus node arrests, isoflurane was discontinued. In each case, normal sinus rhythm returned within minutes. When isoflurane was reinstituted in three of those animals, sino-atrial block recurred within minutes.

Discussion

Critique of Methods

The protocol employed was designed to simulate the clinical situation in which, during ongoing surgery, patients receiving diltiazem receive a baseline anesthetic to which isoflurane is subsequently added to either deepen the anesthetic state or to deliberately induce hypotension. Plasma levels of diltiazem achieved in this study have been shown to be clinically relevant.[27-29] The type and amount of premedication and baseline anesthetic were selected to (a) ensure adequate sedation, analgesia, and anesthesia, and (b) to avoid myocardial depression. Premedication with fentanyl and droperidol have little effect on the cardiovascular system.[30] Effective premedication permitted a considerable reduction in induction and maintenance dose of pentobarbital. Its discontinuation at least 2 h prior to the start of the experiment should have minimized or even eliminated[31] myocardial depression. However, some lasting effects of pentobarbital and a potential for later interaction with fentanyl or diltiazem cannot totally be excluded. Fentanyl was not entirely discontinued upon introduction of isoflurane, because this might have resulted in decreasing drug levels throughout the experiment. It has, therefore, to be realized that the effects elicited by diltiazem and isoflurane occurred in the open-chest animal after premedication with droperidol and fentanyl, and during a baseline anesthesia with fentanyl. Negative inotropic influences may be more pronounced in the open-chest than in the closed-chest animal.[32]

Diltiazem and Myocardial Performance

Diltiazem alone had little effect on global right (RVSP, RVSW) and left (LVSW, SV) ventricular myocardial performance. This is in agreement with the results of previous studies, which have shown that diltiazem in therapeutic doses has little effect on inotropy in intact animals as well as in awake subjects.[4,17,33] However, the finding of unchanged indices of LV systolic performance (LV dP/dt_{max}, systolic segment lengths, segment shortening) in the presence of unchanged indices of LV preload (end diastolic segment lengths, LVEDP), unchanged HR, and reduced indices of LV afterload (AoP_m, SVR) is suggestive of some myocardial depression caused by diltiazem. Such direct negative inotropic effects of diltiazem have been demonstrated *in vitro*.[3,17]

Regional RV performance was affected differently from that of the LV. Whereas segment shortening in RV inflow and outflow tract remained equally unaffected, end diastolic as well as systolic segment lengths in both inflow and outflow tract increased. Again, the finding of unchanged systolic shortening in the presence of unchanged indices of RV afterload (PAP_m, PVR) and increased indices of RV preload (end diastolic segment lengths) is suggestive of myocardial depression caused by diltiazem. Differences in RV and LV regional myocardial performances may be related to diltiazem's different effects on RV (unchanged) and LV (reduced) afterloads. These results indicate that global myocardial performance may not necessarily reflect regional myocardial function.

Diltiazem and Coronary, Systemic, and Pulmonary Circulations

Diltiazem proved to be a potent coronary vasodilator. This is in accordance with previous studies.[15,16] Coronary vasodilation may become evident before either negative inotropy or chronotropy develop.[17] CVR decreased approximately twice as much as SVR, and CBF as a percentage of AoF increased to a similar degree. This would suggest that diltiazem is a more potent coronary than systemic vasodilator. This has previously been suggested.[16] In contrast to its vasodilatory effects on the coronary and systemic circulations, diltiazem did not alter PVR. This is in accordance with a previous study.[34]

Diltiazem and Cardiac Rate and Rhythm

In this study, HR did not change significantly. *In vitro*, diltiazem exhibits direct dose-dependent negative chronotropic effects.[3,17,18] In awake subjects, however, HR tends

to decrease only little,[33,35] and in conscious animals there may even be a dose-dependent increase in HR.[17,36] Apparently the *in vitro* suppressive effect of diltiazem on the sinoatrial node is modified considerably *in vivo* by the reflex increase in sympathetic tone as a result of the fall in blood pressure.[18]

Administration of diltiazem resulted in marked electrophysiologic alterations. PR intervals increased in all animals, and II° AV block type I developed in three of the eight animals. This clearly reflects impaired AV conduction. Similar increases in PR intervals at very similar plasma levels of diltiazem have been reported previously.[37,38] This suppressive effect on the AV node is also seen in the clinical setting,[18] but it is less pronounced and, at times, occurs only at considerably higher plasma levels.[35] The dog appears to be more sensitive than the human to the effects of diltiazem on AV conduction. The PR interval might, therefore, be a particularly sensitive indicator of the pharmacological effects of diltiazem in the dog.[37]

QRS interval and QT_c duration remained unchanged during diltiazem. This was to be expected, because the His-Purkinje system and the ventricular muscle are fast channel-dependent tissues in which the inward current is not primarily carried by calcium. This is consistent with the finding of an unchanged ventricular muscle effective refractory period in anesthetized animals at plasma levels which significantly depressed AV nodal function.[37]

Isoflurane and Myocardial Performance

The addition of isoflurane to diltiazem resulted in myocardial depression. As end diastolic pressures and dimensions tended to increase (RV) or remained unchanged (LV), and as indices of afterload remained unchanged (RV) or tended to decrease (LV), the reductions in LV and RV segmental shortening, systolic pressures, and stroke work, in LV dP/dt_{max} and stroke volume, and the increases in systolic dimensions for both RV and LV can only be attributed to the negative inotropy of isoflurane. This is in accordance with previous *in vitro*[39,40] and *in vivo* studies.[12-14,41] However, there were never any qualitative changes in the sonomicrometry signals suggestive of regional myocardial ischemia.[24]

When compared to a previous study using an identical surgical preparation,[13] in this study myocardial depression occurred at much lower isoflurane concentrations. Two mechanisms may be responsible. The first is that, as with calcium entry blockers, volatile anesthetic agents, in general, interfere with normal calcium ion flux within myocardial muscle fibers.[42] In particular, isoflurane causes complex alterations of intracellular calcium control predominantly by the sarcoplasmic reticulum.[11] Additive effects of diltiazem and isoflurane on the myocardium are, therefore, to be expected. Such additive effects on the contractile force have been demonstrated in the isolated guinea pig atria.[21]

The second mechanism possibly involved is the lack of additional peripheral vasodilation in response to isoflurane. Usually, isoflurane alone causes pronounced peripheral vasodilation.[13,14] In the present study, however, SVR remained unchanged. Thus, in the presence of myocardial depression, the LV did not benefit from a simultaneous decrease in afterload. This lack of additional peripheral vasodilation in response to isoflurane may best be explained by diltiazem's preceding peripheral vasodilatory effect. It thus appears that, in the diltiazem pretreated animal, relatively little isoflurane is needed to significantly reduce systemic arterial pressure. Hypotension is now primarily the result of myocardial depression rather than peripheral vasodilation.

Isoflurane and Coronary Hemodynamics

In these diltiazem-pretreated animals, isoflurane caused a decrease in CBF by approximately 45% without changes in CVR. This is in contrast to the results of previous studies, in which isoflurane caused decreases in CVR.[13,14] As in the case of systemic vasodilation, lack of coronary vasodilation in response to isoflurane can best be explained by diltiazem's pronounced preceding coronary vasodilatory effect. It is, therefore, to be expected that patients on diltiazem medication will exhibit very different behavior in coronary hemodynamics during isoflurane-induced hypotension.

Isoflurane and Cardiac Rhythm

The addition of isoflurane to diltiazem resulted reproducibly in pronounced arrhythmias involving primarily sinoatrial nodal function. In isolated SA node cells of guinea pigs, isoflurane slows the spontaneous rate of discharge primarily by its affects on the rate of phase 4 depolarization.[19] Interactions between isoflurane and the slow inward current on one hand, and between isoflurane and diltiazem on the other hand, are therefore to be expected.

In contrast to sinoatrial conduction abnormalities, the mean PR intervals, as well as QRS duration and QT_c intervals, remained unaffected by the addition of isoflurane. This is consistent with the finding that increasing isoflurane has no effect upon AV conduction as determined by His-bundle electrocardiography.[43] However, when compared to the conscious state, modest prolongation (9–12%) of AV nodal conduction time above 1.2 MAC isoflurane has been recently reported.[7]

The effects of diltiazem on cardiovascular function during isoflurane anesthesia have previously been studied.[20] When diltiazem was administered during baseline anesthesia with isoflurane 1.5% at a dose that achieved

comparable diltiazem plasma levels, PR intervals increased by approximately 25%, and three of the 13 animals developed II° AV block type I and one of them junctional escape rhythm. No SA arrests were observed. The addition of diltiazem to isoflurane had little effect on global hemodynamics. However, the finding of an unchanged cardiac output and a decreased LV dP/dt_{max} in the presence of increased cardiac filling pressures and unchanged arterial pressure would suggest that some degree of myocardial depression had developed. This is consistent with our own results. Direct comparison, however, is difficult because of differences in experimental model, in baseline anesthesia, and in sequence of drug administration. Conduction abnormalities and myocardial depression have also been reported when the calcium entry blocker verapamil was added to 1.6% end-tidal concentration of isoflurane.[44]

In summary, our data indicate that diltiazem at clinically relevant plasma levels is a systemic vasodilator and an even more powerful coronary vasodilator. It may cause significant electrophysiologic alterations with only minimal adverse effects on global right and left ventricular myocardial performance. It appears that the response of the systemic and coronary vasculature, as well as the myocardium and the conduction system, to subsequent isoflurane administration is significantly modified by pretreatment with diltiazem. Administration of isoflurane under these circumstances may result in pronounced impairment of SA conduction and myocardial depression. It appears that the depressant effects of diltiazem and isoflurane on myocardial performance and SA function are additive. Therefore, it is possible that patients who receive diltiazem will be sensitive to the subsequent addition of isoflurane.

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