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CARDIOVASCULAR EFFECTS OF DILTIAZEM IN THE DOG

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Despite improvements in the anaesthetic management of patients with coronary artery disease, the occurrence of myocardial ischaemia is still a serious threat during the perioperative period. Ischaemia is usually associated with tachycardia, arterial hypertension, increased wall tension or coronary vasoconstriction [1]. Consequently, the ideal treatment should decrease arterial and ventricular filling pressures, and heart rate, and decrease coronary artery tone without having any adverse effects on myocardial contractility and conduction. Diltiazem is one of the recently-introduced calcium entry blockers available for i.v. use in man. In its oral form it is highly effective in the management of angina pectoris [2]. When administered i.v. to conscious subjects, it is a potent coronary and systemic vasodilator without evidence of untoward effects on heart rate or myocardial contractility [3, 4]. In addition, it possesses antiarrhythmic properties [5, 6], and protects the myocardium from ischaemic and reperfusion injury [7, 8]. Thus it may be well suited for the treatment of perioperative myocardial ischaemia. However, the efficacy and safety of diltiazem during anaesthesia remain to be determined as hypotension, bradycardia and abnormalities of conduction have been reported after i.v. administration in anaesthetized man, and anaesthetized animals [9, 10].

The aim of this study was to investigate the effects of bolus injections and constant infusions of diltiazem on the systemic, pulmonary and coronary circulations, on global and regional left (LV) and right ventricular (RV) function, and on the ECG during neuroleptanaesthesia. Administration of nitroglycerin (TNG) before and after the administration of diltiazem served to assess the effects of anaesthesia and of diltiazem on baroreceptor function.

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SUMMARY

The effects of two bolus injections (0.2 mg kg^{-1}) and two infusion rates (0.2 mg min^{-1} and 0.4 mg min^{-1}) of diltiazem on global and regional left (LV) and right ventricular (RV) performance (ultrasonic dimension technique), on coronary (electromagnetic flow meters) and systemic haemodynamics, and on electrophysiology (PR, QRS, QT_c intervals) were studied in eight open-chest dogs anaesthetized with droperidol and fentanyl. The two bolus injections of diltiazem resulted in plasma concentrations of 688 ± 115 and 650 ± 85 ng ml^{-1} (means ± SE), respectively, and caused substantial decreases in systemic and coronary vascular resistances, and in aortic pressure, and increases in LV segment shortening, stroke volume and aortic flow. Electrophysiological variables were little affected. At the low infusion rate (plasma concentration 140 ± 23 ng ml^{-1}) coronary and systemic vasodilatation occurred, but global and regional RV and LV performance were little affected. PR interval increased by 15%. At the higher infusion rate (plasma concentration 282 ± 33 ng ml^{-1}) coronary and systemic vasodilatation were maintained. Aortic pressure decreased slightly. Whereas LV end-diastolic and end-systolic dimensions remained unchanged, they increased in the RV. In addition, the PR interval increased by 35%, and three animals developed atrioventricular block type I. The data indicate that diltiazem is a potent coronary and systemic vasodilator with little effect on global RV and LV performance. However, at a higher infusion rate RV dimensions clearly tend to increase, and conduction abnormalities develop.

METHODS

Instrumentation

Eight mongrel dogs of either sex weighing between 27 and 33 kg received fentanyl

0.04 mg kg^{-1} and a large dose of droperidol (2 mg kg^{-1}) i.m. 1 h before the induction of anaesthesia. After this premedication the dogs became heavily sedated, recumbent, and did not resist the placement of a peripheral venous cannula. Anaesthesia was induced with small incremental doses of pentobarbitone i.v. up to a maximum total of 10 mg kg^{-1} and then maintained with continuous infusions of pentobarbitone 1 mg kg^{-1} h^{-1} i.v., and fentanyl 20 μg kg^{-1} h^{-1} i.v. Additional bolus doses of fentanyl 500 μg were given i.v. whenever increases in heart rate and arterial pressure, or movements, indicated a decrease in the depth of anaesthesia. The trachea was intubated and controlled ventilation (Harvard constant-volume ventilator, Harvard Apparatus Co., South Natick, MA) facilitated by a continuous infusion of pancuronium 0.04 mg kg^{-1} h^{-1} i.v. Tidal volume was set at 15 ml kg^{-1}. Ventilatory rates and inspired oxygen concentrations were adjusted to maintain the arterial carbon dioxide tension (Pa_{CO_2}) between 4 and 5.3 kPa and the arterial oxygen tension (Pa_{O_2}) between 20 and 46.7 kPa. Positive end-expiratory pressure (2 cm H_2O) was applied to prevent major airway collapse in the open-chest animals. Sodium bicarbonate was administered if the calculated base deficit exceeded 5 mmol $litre^{-1}$. All dogs were in the supine position and placed on a heating element incorporated in the operating table. Body temperature was monitored continuously by the thermistor of a flow-directed thermodilution catheter (Edwards Laboratory, Santa Ana, CA, Model 93-132-5F) inserted through the right jugular vein into the pulmonary artery. All animals received 4–6 ml kg^{-1} h^{-1} of physiological saline i.v.

Catheter-tip manometers (6F, Millar Instruments Inc, Houston, TX) were advanced into the ascending aorta just above the aortic valve, and into the left and right ventricles. The catheter-tip manometers were prewarmed in a water bath at 37 °C for several hours, and they were calibrated simultaneously and immediately before insertion. Calibration was performed by actuating a switch incorporated in the connection cable that produced an electrical output corresponding to a pressure of 100 mm Hg. Baseline stability of the high-fidelity signals was verified repeatedly during the experiment by superimposing the manometer-derived pressures on those derived either from the separate fluid-filled catheter in the aortic arch, or from the fluid-filled lumina incorporated in the RV and LV catheter-tip manometers using Statham transducers (P23 ID). 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 non-occlusive zero (Hellige Co., Freiburg i. Br., West Germany).

Regional myocardial function

Regional myocardial performance was evaluated by sonomicrometry [11, 12]. 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 (RVIT and RVOT). 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, percent segment shortening during systole (ΔSL) was derived [$\Delta SL\ (\%) = (SL_{ed} - SL_{sys})/SL_{ed} \times 100$]. 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. Analysis of aortic flow and pressure signals in several animals showed that zero aortic flow and the dicrotic notch occurred within 40 ms of each other. The ultrasonic signals were also assessed visually for qualitative changes such as akinesis, paradoxical systolic segment lengthening or postsystolic segment shortening.

Haemodynamic measurements

A multichannel recorder (Hellige Co., Freiburg i. Br., West Germany) was used for the continuous recording of all signals. LV dP/dt was derived from LV high-fidelity signals using operational amplifiers connected to a differentiator (Hellige

Co., Freiburg i. Br., West Germany). Right (RVSW) and left ventricular stroke work (LVSW), and stroke volume (SV) were derived from standard formulae. Systemic (SVR), pulmonary (PVR), and right (CVR_R) and left anterior descending (CVR_{LAD}) coronary artery vascular resistances were derived from the following formulae:

$$\text{SVR (dyn s cm}^{-5}) = \frac{\text{MAoP (mm Hg)} - \text{RVEDP (mm Hg)}}{\text{AoF min}} \times 80$$

$$\text{PVR (dyn s cm}^{-5}) = \frac{\overline{P_{PA}}\text{ (mm Hg)} - \text{LVEDP (mm Hg)}}{\text{AoF (litre min}^{-1})} \times 80$$

$$CVR_R \text{ (kdyn s cm}^{-5}) = \frac{\text{MAoP (mm Hg)} - \text{RVEDP (mm Hg)}}{CBF_R \text{ (ml min}^{-1})} \times 80$$

$$CVR_{LAD} \text{ (kdyn s cm}^{-5}) = \frac{AoP_d \text{ (mm Hg)} - \text{LVEDP (mm Hg)}}{CBF_{LAD} \text{ (ml min}^{-1})} \times 80$$

where MAoP = mean aortic pressure, RVEDP = right ventricular end-diastolic pressure, AoF = mean aortic flow, $\overline{P_{PA}}$ = mean pulmonary artery pressure, LVEDP = left ventricular end-diastolic pressure, CBF_R = mean right coronary artery blood flow, AoP_d = end-diastolic aortic pressure, and CBF_{LAD} = mean left anterior descending coronary artery blood flow. Heart rate (HR) was derived from the R–R intervals of an extremity ECG.

Electrocardiographic (ECG) measurements

Lead II of the ECG was recorded continuously and analysed for evidence of arrhythmias and conduction abnormalities. Five consecutive cardiac cycles recorded at end-expiration at a chart speed of 100 mm s^{-1} were used for the measurements of the PR, QRS and QT intervals. QT_c intervals were calculated according to the formula:

$$QT_c = \frac{QT}{\sqrt{RR}}$$

where RR = cycle length of ECG (s).

Experimental programme

After sternotomy, and approximately 2 h before the start of the experiment, pentobarbitone was discontinued. Any adjustments in ventilation, acid–base status, depth of anaesthesia, and fluid administration were made no later than 30 min before the start of the definitive study.

Hydrophilized diltiazem hydrochloride dissolved in distilled water was freshly added to 0.9 % sodium chloride to yield concentrations of 1 mg ml^{-1} and 0.4 mg ml^{-1} for bolus injection and continuous infusion, respectively. Commercially available i.v. nitroglycerin (Trinitrosan, Merck) 5 mg ml^{-1} was diluted in 0.9 % sodium chloride to obtain a concentration of 50 μg ml^{-1}.

Following control readings a bolus dose of TNG 5 μg kg^{-1} was administered. After the return of all measured variables to control values (C), a bolus dose of diltiazem 0.2 mg kg^{-1} was administered. This was followed by a continuous infusion (0.2 mg min^{-1}) which was maintained for 30 min. Immediately after the measurements, a further i.v. bolus of diltiazem 0.2 mg kg^{-1} was given, and the infusion rate was doubled to 0.4 mg min^{-1} and maintained at this rate for 30 min. Finally, an additional bolus of TNG 5 μg kg^{-1} was administered. Measurements following the bolus injections of TNG and diltiazem were made at the time of the lowest AoP which occurred within 1 min of injection. Measurements during the infusions were made during steady-state conditions at the end of each of the two 30-min infusion periods of diltiazem (0.2 mg min^{-1} = $D1_{inf}$; 0.4 mg min^{-1} = $D2_{inf}$).

Arterial blood was sampled during C and at the end of each diltiazem infusion period for determinations of haematocrit (Hct) (Microcentrifuge Compur, Munich, West Germany, Model M1100), arterial blood-gas tensions and arterial pH (Instrumentation Laboratory, Lexington, MA, Model 613), and plasma concentrations of diltiazem. Additional measurements of diltiazem plasma concentrations were obtained following the two bolus injections. Diltiazem was assayed by electron-capture gas–liquid chromatography. As internal standard the butyryl analogue of diltiazem was used. This method has an overall sensitivity of less than 5 ng/ml of plasma [13].

Statistical analysis

The data were analysed statistically 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 paired comparisons [14]. A P value of < 0.05 was considered significant.

TABLE I. *Effects of diltiazem on systemic haemodynamics and left ventricular function (mean ± SE). C = control; $D1_{bol}$ and $D2_{bol}$ = first and second i.v. bolus injection of diltiazem 0.2 mg kg^{-1}; $D1_{inf}$ and $D2_{inf}$ = infusions of diltiazem 0.2 mg min^{-1} and 0.4 mg min^{-1}, respectively. $LVSL_{ed}$ = left ventricular (LV) end-diastolic segment length; $LVSL_{sys}$ = LV systolic segment length; ΔLVSL = LV systolic segment shortening; LVEDP = LV end-diastolic pressure; MAoP = mean aortic pressure; HR = heart rate; AoF = aortic flow; SV = stroke volume; LVSW = LV stroke work; SVR = systemic vascular resistance. †P < 0.05 when compared with C; *P < 0.05 when compared with preceding value; §P < 0.05 when $D2_{inf}$ compared with $D1_{inf}$*

Variable	C	$D1_{bol}$	$D1_{inf}$	$D2_{bol}$	$D2_{inf}$
$LVSL_{ed}$ (mm)	9.2±0.4	9.1±0.4	9.2±0.2	9.4±0.3	9.4±0.3
$LVSL_{sys}$ (mm)	6.3±0.3	5.8±0.4†	6.1±0.3	5.8±0.3	6.3±0.2
ΔLVSL (%)	31.2±2.7	35.4±3.8†	33.1±2.7	38.7±3.5†*	32.5±2.9
LVEDP (mm Hg)	5.9±0.4	5.7±0.4	5.8±0.4	5.9±0.6	6.2±0.7
MAoP (mm Hg)	94±3	75±4†	92±4*	75±4†*	88±2†*
LV dP/dt_{max} (mm Hg s^{-1})	2492±163	2521±183	2531±172	2598±222	2492±185
HR (beat min^{-1})	94±6	103±6†	97±6*	97±4	94±6
AoF (litre min^{-1})	2.0±0.2	2.5±0.2	2.3±0.2	2.6±0.3†*	2.3±0.3
SV (ml beat^{-1})	22±2	24±2†	24±3	26±3†*	25±3†
LVSW (g m)	27±3	23±3†	28±4*	26±4	28±4
SVR (dyn s cm^{-5})	3649±177	2349±78†	3261±152†*	2294±127†*	3127±292†*

TABLE II. *Effects of diltiazem on pulmonary haemodynamics and right ventricular function (mean ± SE). $RVITSL_{ed}$ = right ventricular (RV) inflow tract (IT) end-diastolic segment length; $RVISTL_{sys}$ = RVIT systolic segment length; ΔRVITSL = RVIT systolic segment shortening; $RVOTSL_{ed}$ = RV outflow tract (OT) end-diastolic segment length; $RVOTSL_{sys}$ = RVOT systolic segment length; ΔRVOTSL = RVOT systolic segment shortening; RVEDP = RV end-diastolic pressure; RVSP = RV systolic pressure; $P\overline{PA}$ = mean pulmonary artery pressure; RVSW = RV stroke work; PVR = pulmonary vascular resistance. (See table I for further abbreviations)*

Variable	C	$D1_{bol}$	$D1_{inf}$	$D2_{bol}$	$D2_{inf}$
$RVITSL_{ed}$ (mm)	10.3±0.6	10.7±0.6†	10.4±0.6	10.9±0.7†*	10.8±0.7†§
$RVITSL_{sys}$ (mm)	8.1±0.6	8.3±0.6	8.2±0.6	8.4±0.7†	8.4±0.7†
ΔRVITSL (%)	22.0±1.4	22.9±2.0	21.6±1.9	23.3±1.9	22.7±1.7
$RVOTSL_{ed}$ (mm)	10.5±0.8	10.9±1.0†	10.9±1.0†	11.3±1.0†*	11.3±0.9†
$RVOTSL_{sys}$ (mm)	8.0±0.7	8.2±0.8	8.2±0.7	8.4±0.8†	8.4±0.7†
ΔRVOTSL (%)	24.1±1.7	25.7±1.5	25.1±1.5	25.6±1.1	25.7±1.6
RVEDP (mm Hg)	3.6±0.3	4.1±0.4	3.9±0.3	4.5±0.4†*	3.9±0.3
RVSP (mm Hg)	29±2	30±1	30±2	31±2	29±2
$P\overline{PA}$ (mm Hg)	13±1	14±1	13±1	14±1	14±1
RVSW (g m)	2.9±0.6	3.4±0.7†	3.0±0.5	3.6±0.6†*	3.5±0.6§
PVR (dyn s cm^{-5})	274±31	275±25	274±33	267±26	280±34

RESULTS

Effects of bolus injections of diltiazem on systemic and pulmonary haemodynamics, and on RV and LV function (tables I and II)

The two bolus injections of diltiazem resulted in plasma concentrations of 688±115 ($D1_{bol}$) and 650±85 ng ml^{-1} ($D2_{bol}$), respectively. The first bolus injection ($D1_{bol}$) caused a decrease in MAoP accompanied by increases in HR and AoF, and a decrease in SVR and LVSW. LVEDP and LV dP/dt_{max} remained unchanged. $LVSL_{sys}$ decreased, and ΔLVSL increased. In contrast to the response of the LV and the systemic circulation, $RVIT_{ed}$ and $RVOT_{ed}$ increased; ΔSL did not change. RV systolic pressure (RVSP), $P\overline{AP}$ and RVSW tended to increase, and PVR remained unchanged.

In contrast to $D1_{bol}$, the second bolus injection ($D2_{bol}$) given at the end of the lower-dose infusion had no effect on HR, despite a similar decrease in MAoP. It caused additional increases in $RVITSL_{sys}$ and $RVOTSL_{sys}$, and in RVEDP. All other effects were comparable to $D1_{bol}$.

TABLE III. *Effects of diltiazem on left and right coronary haemodynamics (mean ± SE). CBF_{LAD} = mean left anterior descending coronary artery blood flow; CBF_R = mean right coronary artery blood flow. (See table I for further abbreviations)*

Variable	C	$D1_{bol}$	$D1_{inf}$	$D2_{bol}$	$D2_{inf}$
CBF_{LAD} (ml min^{-1})	27 ± 3	43 ± 7†	32 ± 4†*	43 ± 6†*	36 ± 5†*§
CBF_R (ml min^{-1})	14 ± 2	25 ± 3†	18 ± 2†*	26 ± 3†*	21 ± 2†*§
CVR_{LAD} (kdyn s cm^{-5})	241 ± 23	115 ± 17†	194 ± 23†*	111 ± 15†*	171 ± 24†*§
CVR_R (kdyn s cm^{-5})	530 ± 40	257 ± 36†	406 ± 37†*	242 ± 36†*	343 ± 39†*
CBF_{LAD}/HR (µl $beat^{-1}$)	286 ± 32	412 ± 53†	330 ± 37†*	442 ± 55†*	380 ± 51†§
CBF_R/HR (µl $beat^{-1}$)	154 ± 16	237 ± 26†	187 ± 19†*	267 ± 31†*	222 ± 18†*§
CBF_{LAD}/AoF · 100 (%)	1.32 ± 0.13	1.74 ± 0.21†	1.51 ± 0.21	1.76 ± 0.23†	1.69 ± 0.27§
CBF_R/AoF · 100 (%)	0.72 ± 0.06	1.01 ± 0.11†	0.86 ± 0.11†*	1.07 ± 0.13†*	0.99 ± 0.13†

There were no qualitative changes in sonomicrometry signals—such as akinesis or paradoxical systolic segment lengthening.

Effects of bolus injections of diltiazem on coronary haemodynamics (table III)

Following $D1_{bol}$ there were pronounced increases in coronary blood flow (CBF), in CBF per heart beat (CBF/HR) and in CBF expressed as a fraction of AoF (CBF/AoF), and a decrease in CVR. These responses were clearly blunted during $D2_{bol}$.

Effects of the infusion of diltiazem on systemic and pulmonary haemodynamics, and on LV and RV function (tables I and II)

The two infusion rates of diltiazem resulted in plasma concentrations of 140 ± 23 ng ml^{-1} ($D1_{inf}$) and 282 ± 33 ng ml^{-1} ($D2_{inf}$), respectively. Except for a slight decrease in SVR, the low infusion rate ($D1_{inf}$) had no significant effects on systemic haemodynamics or LV function. At the higher infusion rate ($D2_{inf}$) there was a small (7%) decrease in MAoP, and increases (13%) in SV and AoF. However, when compared with each other there were no differences between $D1_{inf}$ and $D2_{inf}$. Except for an isolated increase in $RVOTSL_{ed}$, $D1_{inf}$ had no significant effect on RV function or on the pulmonary circulation. At the higher infusion rate ($D2_{inf}$), however, end-diastolic and end-systolic dimensions of RVIT and RVOT, and RVSW increased without changes in segment shortening. $\overline{PAP}$ and PVR remained unchanged throughout. As with the bolus doses, there were no qualitative changes in the sonomicrometry signals.

Effects of the infusion of diltiazem on left and right coronary haemodynamics (table III)

During both infusion periods there were marked increases in CBF, in the amount of coronary blood flow per heart beat (CBF/HR) and in the ratio of CBF and AoF (CBF/AoF), accompanied by similar decreases in CVR.

Correlation between plasma concentrations of diltiazem and haemodynamic effects

There were significant negative correlations between the plasma concentrations of diltiazem and changes in MAoP ($r = -0.62$, $P < 0.01$), SVR ($r = -0.65$, $P < 0.01$), CVR_{LAD} ($r = -0.58$, $P < 0.01$) and CVR_R ($r = -0.38$, $P < 0.05$).

Effects of diltiazem on cardiac rhythm and electrophysiological variables (table IV)

QRS and QT_c intervals remained unchanged throughout. During the infusions and following the second bolus injection, the PR interval increased. Three of the eight animals developed second degree atrioventricular block type I (Wenckebach) during the infusion of diltiazem at the higher rate.

Effects of TNG (table V)

The two bolus injections of TNG administered either before (TNG_1) or after (TNG_2) the second diltiazem infusion resulted in similar decreases (30%) in MAoP and similar increases (20–25%) in HR.

Changes in pHa, Pa_{O_2}, Pa_{CO_2}, Hct and temperature were minimal throughout the experiment (table VI).

TABLE IV. *Effects of diltiazem on electrocardiographic variables (mean ± SE). (See table I for further abbreviations)*

Variable	C	$D1_{bol}$	$D1_{inf}$	$D2_{bol}$	$D2_{inf}$
PR (s)	0.14±0.01	0.13±0.01	0.16±0.01†*	0.15±0.01†	0.19±0.02†*
QRS (s)	0.08±0.01	0.07±0.01	0.07±0.01	0.07±0.01	0.07±0.01
QT_c (s)	0.33±0.01	0.34±0.01	0.32±0.01	0.32±0.01	0.33±0.01

TABLE V. *Effect of nitroglycerin-induced hypotension on heart rate before and after diltiazem (mean ± SE). TNG_1, TNG_2 = nitroglycerin (TNG) 5-μg kg^{-1} bolus administered before (TNG_1) and after (TNG_2) diltiazem infusion ($D2_{inf}$). *P < 0.05 when compared with the preceding value. (See table I for further abbreviations)*

Variable	C	TNG_1	$D2_{inf}$	TNG_2
MAoP (mm Hg)	96±3	68±4*	88±2	63±3*
HR (beat min^{-1})	91±7	117±6*	94±9	114±4*

TABLE VI. *Effects of experimental procedure on general homeostasis (mean ± SE). (See table I for further abbreviations)*

Variable	C	$D1_{inf}$	$D2_{inf}$
pHa	7.37±0.01	7.37±0.01	7.37±0.01
Pa_{O_2} (kPa)	33.1±2	31.6±2.53	31.2±2.93*
Pa_{CO_2} (kPa)	5.1±0.13	4.9±0.13†	4.8±0.13†
Hct (%)	35±1	37±1†	38±1†
Temp. (°C)	37.6±0.2	37.6±0.2	37.6±0.2

DISCUSSION

The purpose of this study was to examine the effects of i.v. administration of diltiazem on the cardiovascular system during neuroleptanaesthesia.

Diltiazem i.v. at clinically relevant plasma concentrations caused substantial systemic and coronary vasodilatation, and it enhanced LV pump function. At the same time, however, diltiazem caused dose-dependent prolongation of atrioventricular conduction. There were important differences between the effects of the bolus injections and the infusions of diltiazem, and differences between the effects on RV and LV function and on the different circulations.

Critique of methods

The design of the study simulated the clinical situation in which diltiazem is given to patients undergoing open heart surgery. In addition, the second bolus injection of diltiazem, given on top of the lower rate infusion, approximated the clinical situation in which those patients receiving diltiazem before operation receive an additional dose during the operative procedure.

Clinically relevant plasma concentrations of diltiazem were achieved during both infusion rates [15, 16]. The bolus injections resulted in considerably higher values. The plasma concentrations after the second bolus injection were lower than expected and statistically not different from those found after the first bolus. At present we have no explanation for this finding.

The cardiovascular effects of a calcium entry blocker given during operation depend on the interactions with the anaesthetic drugs used and on the baseline conditions of the circulation. In this study the anaesthesia was based on droperidol given in a large dose i.m. before induction of anaesthesia, and on fentanyl given as a continuous infusion and supplemented with additional bolus doses when required. While adverse interactions have been described between diltiazem and inhalation anaesthetic agents [10, 17, 18], the effects of diltiazem during i.v. anaesthesia have not been studied as yet. The baseline haemodynamic status was characterized by a normal heart rate, a normal arterial pressure and a slightly decreased aortic flow. This haemodynamic pattern closely resembles the clinical situation following sternotomy and pericardiotomy [19]. The discontinuation of pentobarbitone 2 h before the measurements should have minimized myocardial depression [20], but, with regard to the long elimination half-time of pentobarbitone, a potential for later interactions cannot be totally excluded. In addition, negative inotropic influences may be more pronounced in the open-chest than in the closed-chest animal [21]. Nevertheless, the lower baseline aortic flow appears to be primarily the result of the opening of the chest, positive pressure ventilation, and reductions in venous return and ventricular filling.

On the other hand, normal heart rates and arterial pressures during the control period indicate that there was no inappropriate sympatho-

adrenergic stimulation. The responsiveness of the autonomic nervous system, however, was well maintained, as demonstrated by the baroreflex-mediated tachycardia after nitroglycerin.

Effects of diltiazem on systemic and pulmonary circulations

Diltiazem proved to be a potent systemic vasodilator. This is in accordance with previous studies [3, 22]. Except during the low-dose infusion, the reductions in SVR were accompanied by a decrease in AoP. In contrast, diltiazem did not alter PVR and $\overline{P}_{AP}$. Similar results have been reported previously [9, 23–25].

Coronary circulation

Diltiazem proved to be a potent coronary vasodilator. A direct vasodilatory effect appeared to dominate, since CBF and CBF/HR increased in the presence of decreases in coronary perfusion pressure and evidence of reduced myocardial oxygen demand.

The changes in the coronary circulation were more pronounced than the respective changes in the systemic circulation (fig. 1). This would indicate that diltiazem is an even more powerful coronary, than systemic, vasodilator. This has previously been suggested [26]. The effects of diltiazem on the coronary circulation appear to vary with the baseline anaesthetic. In contrast to the results of this study, CVR did not change in dogs anaesthetized by isoflurane or enflurane [17, 18].

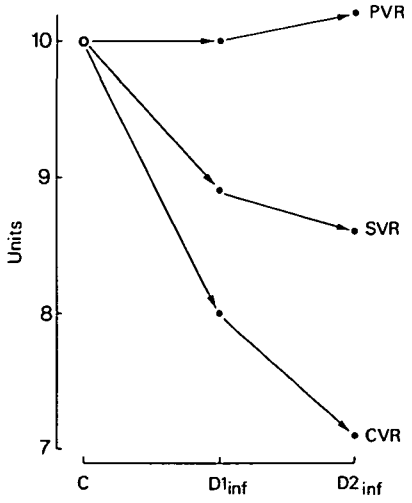

FIG. 1. Changes in pulmonary (PVR), systemic (SVR), and left anterior descending coronary artery vascular resistances (CVR) from control (C) to the first infusion rate of diltiazem ($D1_{inf}$) and from $D1_{inf}$ to the second infusion rate of diltiazem ($D2_{inf}$). Mean values during control have all been standardized to an initial value of 10. There was a significant difference ($P < 0.05$) between the changes of PVR and CVR. SVR tended ($P < 0.1$) to respond less than CVR and more than PVR to the infusion of diltiazem.

Diltiazem and ventricular performance

Diltiazem had no adverse effects on global right (RVSP, RVSW) or left (AoF, SV, LVSW) ventricular performance. This is in agreement with results of previous studies which have shown that, in therapeutic doses, diltiazem has little effect on inotropy in intact animals or in awake man [3, 27]. However, when looking at our data in greater detail, differences in the response to diltiazem between RV and LV, and in the effects of bolus injections and infusions become apparent. Segment shortening and stroke volume increased following the bolus injections, but no such effects were noted during the low-dose infusion, and were less prominent during the high-dose infusion. There are several possible explanations for this difference. First, the decreases in SVR were more pronounced following the bolus injections. At constant preload, a decrease in SVR tends to increase the volume ejected from and returning to the LV [28]. This can be viewed as an upward shift of the LV function curve [29] and could explain the improved LV pump function.

Second, because of the greater decrease in MAoP following the bolus injections, there might have been a more pronounced baroreflex-mediated increase in sympathetic outflow, resulting in increased contractility. However, the findings of an unchanged LV dP/dt, and an unchanged HR, following the second bolus injection do not support such a mechanism.

Third, during the infusions of diltiazem some myocardial depression might have outweighed the beneficial effects of a decrease in afterload on LV function. A direct negative inotropic effect of diltiazem has been demonstrated *in vitro* [27].

The fact that no such effect was noted following the bolus injections, despite considerably higher plasma concentrations, can best be explained by a greater baroreflex-mediated increase in sympathetic tone or the counterbalancing effect of a greater decrease in LV afterload.

The LV end-diastolic dimension and pressure remained unchanged throughout. The systemic

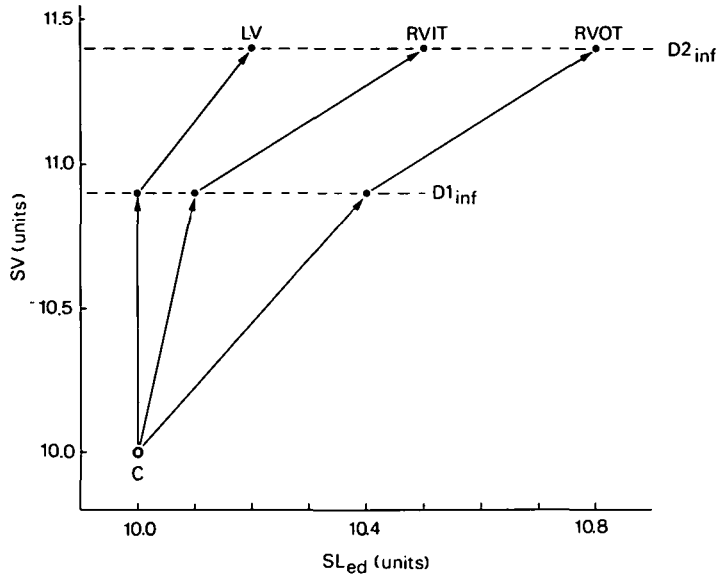

FIG. 2. Plot of end-diastolic segment lengths (SL_{ed}) *v.* stroke volume (SV). Mean values during control (C) have all been standardized to an initial value of 10. The arrows indicate the directional changes from control to the first infusion rate of diltiazem ($D1_{inf}$), and from $D1_{inf}$ to the second infusion rate of diltiazem ($D2_{inf}$). Note the differences in slopes of the SV–SL_{ed} relationship between left and right ventricle. There is a trend ($P < 0.1$) to right- and downward shift of the SV–SL_{ed} relationship in the RVIT and RVOT when compared with LV.

vasodilatation, however, usually shifts the diastolic pressure–volume curve of the LV downwards [30]. Correspondingly, in the presence of an unchanged LV end-distolic dimension (and volume), the LVEDP should have decreased.

Several factors may be responsible for the absence of any changes in LVEDP. First, the increase in flow associated with systemic vasodilatation will increase the diastolic filling rate and, consequently, also the viscous component of the LV compliance [31]. Second, profound coronary vasodilatation may increase the LV wall volume relative to LV chamber volume [32]. Third, an increase in RV end-diastolic dimensions may decrease the LV distensibility by the mechanism of ventricular interdependence [33]. All three factors would counterbalance the effects of an acute reduction in afterload on the LV pressure–volume relation by shifting it in the opposite direction. The net result would be an unchanged LVEDP (as observed), despite substantial changes in LV afterload.

Compared with the LV, the RV operated under clearly different loading conditions. Indices of RV preload (end-diastolic dimensions and pressure) increased and indices of RV afterload ($\bar{P}_{AP}$, PVR) remained unchanged. In contrast to the LV, the increase in output was associated with an increase in preload (fig. 2). It remains to be determined whether this represents an upward shift along the same ventricular function curve, or a right- and downward shift to a different ventricular function curve, indicating myocardial depression. Differences in RV and LV regional myocardial performance are probably related to the different effects of diltiazem on the afterload of the RV (unchanged) and on that of the LV (reduced). This could have potentially important clinical implications for patients receiving diltiazem in the presence of increased RV afterload.

In contrast to the preservation of global RV and LV function during fentanyl anaesthesia noted in this study, in the presence of volatile anaesthetics, diltiazem has been shown to be a potent myocardial depressant [10, 17, 18]. This might have been the result of absence of afterload reduction, underlying myocardial depression caused by inhalation anaesthetics or impaired baroreceptor reactivity. In the present study, the increase in HR following the bolus injections of nitroglycerin indicated that baroreceptor function was preserved, even during the high-dose infusion

of diltiazem. It is, therefore, to be expected that the net haemodynamic response to diltiazem will depend on the kind of application (bolus *v.* infusion), the state of wakefulness (awake *v.* anaesthetized), and the baseline anaesthetic (i.v. *v.* inhalation).

Diltiazem and cardiac rate and rhythm

We observed a dose-dependent increase in the duration of the PR interval during the infusion of diltiazem. This observation is in agreement with other experimental and human studies: diltiazem has a profound effect on sinus and atrioventricular pacemakers, both nodes being slow calcium channel dependent tissues [34].

Except for a 10% increase following the first bolus injection, HR remained unaffected. *In vitro*, diltiazem exhibits direct dose-dependent negative chronotropic effects [27, 34]. In awake subjects, however, HR tends to decrease minimally [3, 35], and in conscious animals there may even be a dose-dependent increase in HR [27, 36]. As the increase in HR following the first bolus injection of diltiazem indicates, the suppressant effect of diltiazem on the sinoatrial node *in vitro* is apparently modified *in vivo* by the reflex increase in sympathetic tone which results from the decrease in arterial pressure [34]. Moreover, pancuronium was used in this study and might antagonize the negative chronotropic effect of diltiazem [37]. As suggested by the absence of any increase in HR in response to the second bolus injection, at high plasma concentrations direct negative chronotropic effects may suppress the reflex increase in HR.

Diltiazem caused progressive alterations in electrophysiological variables. During both infusions the PR intervals increased in a dose-dependent manner and, during the high infusion rate, three animals developed atrioventricular block. This clearly reflects impaired atrioventricular conduction. However, the development of atrioventricular block might be limited by the facilitating effect of pancuronium on atrioventricular conduction [37]. Similar increases in PR interval and similar arrhythmias at similar plasma concentrations have been reported previously [6, 38, 39]. This suppressant effect on the atrioventricular node is also seen clinically [34], but it is less pronounced and, at times, occurs only at considerably higher plasma concentrations [35]. On the other hand, during isoflurane anaesthesia in dogs, PR intervals increased at considerably lower plasma diltiazem concentrations [17]. Despite five-fold higher plasma concentrations after the bolus injections (rather than during the infusion) PR intervals did not increase following either bolus injection. This might have been because of a greater reflex increase in sympathetic tone in response to the more pronounced decrease in arterial pressure.

The durations of the QRS interval and QT_c remained unchanged throughout. This was to be expected because, in contrast to the slow calcium channel-dependent tissues of sinus and atrioventricular nodes, the His-Purkinje system and the ventricular muscle are fast channel-dependent tissues in which the inward current is not primarily carried by calcium ions. This is consistent with the finding of an unchanged ventricular muscle effective refractory period in anaesthetized animals at plasma concentrations which significantly depressed antrioventricular node function [38].

Clinical implications

Diltiazem proved to be a potent coronary and systemic vasodilator without adverse effects on heart rate and global pump function. Consequently, under similar clinical conditions (for example, open heart surgery during neuroleptanaesthesia), diltiazem might improve myocardial oxygen balance by decreasing oxygen demand and increasing oxygen supply. Our results were obtained in animals with presumed normal coronary arteries and myocardium, and the results cannot be extrapolated directly to patients with coronary artery disease. However, beneficial effects of diltiazem have been demonstrated in different types of experimental ischaemia [40–45]. These data indicate that diltiazem may be suitable for the treatment of perioperative ischaemia. Moreover, diltiazem has been shown to prevent sympathetically-mediated constriction of normal and diseased coronary arteries in man [46]. This effect may be important in preventing coronary vasoconstriction and myocardial ischaemia as a result of sympathetic stimulation during the perioperative period. However, some of the beneficial effects of diltiazem may be lost during the infusion of high doses as a result of the development of clinically relevant myocardial depression and abnormalities of conduction. Therefore, bolus injections of diltiazem might be preferable.

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