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Effect of lignocaine in myocardial contusion: an experiment on rabbit isolated heart

[1]Qian Pu, [3]Jean Xavier Mazoit, Lin Sen Cao, [2]Wieke Mao & Kamran Samii

Laboratoire d'Anesthésie, Faculté de Médecine du Kremlin-Bicêtre, Université de Paris-Sud, Le Kremlin-Bicêtre, France

1 The reported incidence of myocardial contusion after blunt chest trauma varies from 16 to 76%. Of these patients, about 6% present a severe, life threatening contusion. We used an isolated heart preparation to examine the effect of lignocaine on myocardial performance after contusion.

2 Thirty hearts obtained from male New Zealand rabbits were perfused at constant flow according to the Langendorff technique and were divided into four groups. The following parameters were measured at frequent intervals for 60 min: mean coronary perfusion pressure (CPP), left ventricular diastolic pressure (LVDP), developed pressure (DP), dP/dt_{max}, dP/dt_{min}.

3 Group 1 ($n=6$) served as control, group 2 ($n=7$) received lignocaine for 20 min (15 μM for the first 10 min and 30 μM for the following 10 min), group 3 ($n=9$) had a contusion leading to a 30–50% decrease in dP/dt_{max} and group 4 ($n=8$) had the contusion and the lignocaine infusion was started 10 min after the contusion and stopped after 30 min. Lignocaine concentration was measured in the effluent.

4 Lignocaine alone moderately decreased contractility in group 2. In group 3, after contusion, DP, dP/dt_{max}, and dP/dt_{min} were markedly decreased during the 60 min recording period. In group 4, lignocaine infusion rapidly restored contractility. DP, dP/dt_{max} and dP/dt_{min} returned towards their basal values. This improvement of contractility remained stable, even after lignocaine infusion was discontinued.

5 In our rabbit isolated heart preparation, lignocaine at a low therapeutic concentration was able to restore contractility after contusion. These results need to be confirmed by other studies but this may lead to promising therapeutic intervention.

Keywords: Local anaesthetics; lignocaine; blunt chest trauma; myocardial contusion; isolated organ; Langendorff

Introduction

The reported incidence of myocardial contusion after blunt chest trauma varies from 16% to 76% (Fabian *et al.*, 1988; 1991; Jackimczyk, 1993). These discrepancies, which are likely to be due to the variability in diagnosis criteria, may explain the wide range of severity described in the literature (Fabian *et al.*, 1988; 1991; Jackimczyk, 1993; Biffl *et al.*, 1994). In fact the use of echocardiography and pulsed Doppler have shown that myocardial dysfunction may appear in about 30% of patients with closed chest trauma (Hiatt *et al.*, 1988; Karalis *et al.*, 1994). It seems that isolated life threatening contusion to the myocardium may occur in about 3–6% of the patients suffering from severe blunt chest trauma (Karalis *et al.*, 1994; Malangoni *et al.*, 1994). Apart from cardiac failure, blunt injury to the heart muscle can result in a variety of dysrhythmias (Fabian *et al.*, 1991; Cachecho *et al.*, 1992; Malangoni *et al.*, 1994) and to ischaemia related in a few cases to direct coronary artery injury (Jackimczyk, 1993; Malangoni *et al.*, 1994). In comparison with the great number of clinical studies already published, few animal experiments have been conducted. However, these experiments have shown that myocardial contusion has two components: (1) direct damage to the muscle with a decrease in myocardial contractile force and (2) an effect on the coronary vascular bed (Anderson and Doty, 1975; Liedtke *et al.*, 1980; Desiderio, 1986; Baxter *et al.*, 1988; Harley *et al.*, 1993).

Treatment of cardiac failure is not easy in these patients with associated injuries. Specific injuries including acute myocardial rupture, valvular disruption or isolated cardiac tamponade require emergency surgical treatment. For the other patients, the usual therapeutic algorithm includes fluid therapy and adrenergic support (Malangoni *et al.*, 1994). However, the use of catecholamines may precipitate severe arrhythmias in these patients. In cases of isolated arrhythmias, lignocaine has been used (Ritchie and Greene, 1990; MacLean *et al.*, 1992; Zipes, 1992), and to our knowledge, despite the slight negative inotropic action of lignocaine (Marzilli *et al.*, 1979; Lynch, 1986), no adverse effects have been reported in these patients. It is also our clinical experience that this drug has no deleterious effect in patients with cardiac contusion, and even may be of benefit in these patients. We therefore decided to study the effect of lignocaine on a rabbit Langendorff preparation with a myocardial contusion.

Methods

Langendorff preparation

All experiments used a modification of a previously described rabbit isolated heart model (Mazoit *et al.*, 1990). Care of the animals conformed to the recommendations of the Helsinki Declaration and to the guidelines of the French law for animal experiments (accreditation number 1989/2559). Thirty male New Zealand rabbits weighing 1800–2200 g were assigned to one of four groups (see below for the description of groups). The rabbits were anaesthetized with urethane, 2.5 g kg^{-1}, i.p. and received heparin (1000 u, i.v.). A tracheotomy was performed, and the animals were ventilated. The chest was opened, and the heart was removed and quickly mounted on the perfusion apparatus. The aorta was cannulated and the

[1] On leave from: Department of Cardiology, Kunming Medical School, Kunming, Yunnan, China.
[2] On leave from: Department of Anaesthesia, Tongji Medical School, Wuhan, China.
[3] Author for correspondence at: Laboratoire d'Anesthésie, Faculté de Médecine, 63 rue Gabriel Péri, F-94276 Le Kremlin-Bicêtre Cedex, France.

heart retrogradely perfused at a constant flow of 20 ml min^{-1} with a modified Krebs-Henseleit buffer. The buffer composition consisted of (mM): NaCl 118, KCl 4.7, $CaCl_2$ 1.8, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25, glucose 5.5, Na pyruvate 2.0, hydroxy-ethyl-starch 12 g l^{-1} and bovine serum albumin 2 g l^{-1}. Salts for the buffer composition (Prolabo, Paris France) were at least of analytical grade and were also compatible with cell culture. Hydroxy-ethyl-starch (Elohes) (average mol. wt. 200,000) was purchased from Laboratoires Biocedra Louviers, France. Bovine serum albumin (A-9647) was purchased from Sigma St Quentin-Fallavier France. The buffer was oxygenated (95% O_2/5% CO_2) by using a hollow fibre oxygenator (Centrysystem 200 HG, Cobe, Les Ulis, France). The quality of oxygenation was regularly tested with a P_{O_2} of 504 ± 29 mmHg (mean $\pm$ s.d.), a P_{CO_2} of 39 ± 1.6 mmHg and a pH of 7.37 ± 0.06. The hearts were paced atrially with a bipolar electrode at a cycle interval of 350 ms (170 beats min^{-1}) by a 0198 Jansen ST stimulator. A small needle was inserted through the left ventricular free wall and the hearts with significant aortic valve regurgitation were not studied.

A compliant balloon catheter (Hugo Sachs Electronik, March-Hugstetten, Germany) was inserted into the left ventricle through the left atrium. After a 15 min stabilization period, the balloon was inflated with increasing volumes of water in order to obtain a Frank-Starling pressure curve, and then deflated to a volume corresponding to 60–70% of peak pressure (usually 0.6–0.8 ml) (Ezzaher *et al.*, 1991). The volume of the balloon was not modified until the end of the experiment. Left ventricular pressure and coronary perfusion pressure were measured with a Statham P20 transducer and recorded on a Gould 8000s chart recorder. The first derivative of left ventricular pressure (dP/dt) was obtained by electronic differentiation. In the hearts receiving lignocaine, the drug was infused just before the aorta via a syringe pump. The pulmonary artery was cannulated for collection of the effluent perfusate, the coronary effluent flow, measured from the pulmonary artery, was 20 ml min^{-1}. Lignocaine was measured in the effluent before lignocaine infusion and at frequent intervals until the end of experiment (Mazoit *et al.*, 1990). The absence of non-specific adsorption on tubing was regularly tested.

Mechanism of injury and experimental protocol

We used the model developed by Baxter (Baxter *et al.*, 1988) for producing a standardised global injury to the myocardium. In brief, a pendulum weighing 180 g was released from a height of 20–25 cm according to the rabbit weight. The blow was given in the antero-posterior position with the heart maintained against an immobile plate. The goal was to obtain a 30–50% decrease in maximum dP/dt two minutes after the blow. Four groups of rabbits were studied. Group one hearts ($n=6$) served as control group, group two hearts ($n=7$) received lignocaine (as commercial hydrochloride salt [Astra, France]), but had no contusion, group three hearts ($n=9$) received the blow, group four hearts ($n=8$) received the blow and the lignocaine infusion. After about 15 min stabilization period, basal measurements were made. The contusion was performed (group 3 and 4) and the parameters were again measured at frequent intervals until 60 min after (Figure 1). Lignocaine (group 2 and group 4) was infused at a rate of 298 μmol min^{-1} (80 μg min^{-1}) from 10 to 20 min after the injury and at a rate of 596 μmol min^{-1} (160 μg min^{-1}) from 20 to 30 min after the injury (Figure 1). These doses corresponded to concentrations of 15 and 30 μM (4 and 8 μg ml^{-1}) in buffer respectively. The first concentration was considered as the upper limit of therapeutic concentration and the second concentration was considered to reflect a mild toxic concentration (Tucker and Mather, 1979); almost all the molecules are free in buffer since the concentration of albumin is very low and no binding occurs on hydroxy-ethyl-starch (unpublished data). We measured the following parameters: left ventricular diastolic pressure (LVDP), left ventricular developed pressure (DP) calculated as the difference between systolic and diastolic pressure, mean coronary perfusion pressure (CPP), maximum and minimum first derivative of the left ventricular pressure (dP/dt_{max} and dP/dt_{min}).

Exclusion criteria

We used the following stability criteria for the Langendorff preparation: (1) the absence of any aortic valve regurgitation, (2) a sinus rhythm (before pacing) greater than 120 beats min^{-1} and lower than 170 beats min^{-1} without arrhythmias and (3) a dP/dt_{max} greater than 1000 mmHg s^{-1}. On the other hand, any heart with an asymmetric injury (by visual inspection) or a fall in dP/dt_{max} lower than 30% or greater than 50% two minutes after the contusion was excluded.

Statistical analysis

Demographic data and basal values were compared between the four groups using ANOVA. The preparation stability was checked in the control group (group 1) for LVDP, DP, CPP, dP/dt_{max}, dP/dt_{min} using ANOVA for repeated measures at $t0$, $t2$, $t5$, $t10$, $t15$, $t20$, $t25$, $t30$, $t40$, $t50$, $t60$ (see Figure 1). These times were used throughout the rest of the study, unless specified.

The effects of lignocaine (or of contusion) on the LVDP, DP, CPP, dP/dt_{max}, dP/dt_{min} were compared between group 2 (or group 3) and the control group using ANOVA (two ways, one of which repeated). Since lignocaine infusion was started only ten minutes after the beginning of measurements, the comparison was made from $t10$ to $t60$ with the mean value of the measured parameters between $t0$ and $t10$ used as covariate. The comparison between group 3 and group 4 (contusion and contusion + lignocaine) was made as follows: first, the homogeneity of the effects of contusion was assessed by comparing the two groups at $t0$, $t2$, $t5$, $t10$, using ANOVA (two ways, one of which repeated); thereafter, the two groups were compared at $t10$, $t15$, $t20$, $t25$, $t30$, $t40$, $t50$, $t60$ using ANOVA (two ways, one way repeated, with the value at T0 [basal value of the parameter before the blow on the heart] as covariate).

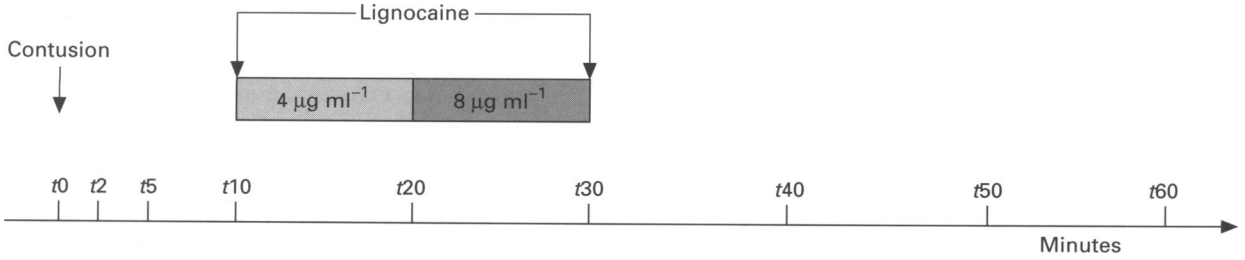

Figure 1 Experimental design. Group 3 and group 4 hearts received a calibrated blow at $t0$. Group 2 and group 4 hearts received lignocaine at two successive infusion rates (arrows). Measurements were done in the four groups at frequent intervals from $t=0$ min to $t=60$ min.

Since it was important to quantify more precisely the differences between the groups, Student's t test with the Bonferroni correction was used for comparing the values at $t20$, $t30$, $t40$, $t50$, $t60$. Data are presented as the mean ± s.e.mean unless specified. $P<0.05$ was considered statistically significant.

Results

The four groups were similar as regards the weight of the rabbit, heart weight, delivered energy and basal parameters (Table 1). The preparation remained stable in the control group for all measured parameters throughout the study period. Left ventricular diastolic pressure was similar in the four groups and did not change significantly with time (Table 1 and Figure 2). Lignocaine was not detected in the effluent perfusate 25 min after lignocaine infusion had been discontinued, in any group.

Effect of lignocaine

In group 2, lignocaine significantly decreased dP/dt_{max} by 21% and dP/dt_{min} by 10% as compared to group 1 and to basal values. LVDP, DP and CPP did not significantly change (Figure 3).

Effect of contusion

Group 3 hearts received a calibrated contusion at $t0$. Just after the blow, the hearts stopped beating during a short period of time (10–60 s). This asystole period was transient and two minutes after the contusion all hearts had totally recovered a paced rhythm without any increase in pacing intensity. At this time, dP/dt_{max} was decreased by 40 ± 5% as compared with the basal value (Figure 4). This decrease in dP/dt_{max} remained constant throughout the 60 min study period (dP/dt_{max} was significantly different from the value measured in the control group and the difference was also significant between repeated measures). The same significant differences were found for dP/dt_{min} and DP. LVDP did not significantly change and in any case LVDP increased after the contusion (Figure 2). CPP increased but the results of ANOVA are not conclusive since no difference was found between group 1 and group 3, whereas there was a significant global increase with time.

Effect of lignocaine after contusion

Group 4 hearts received the blow at $t0$ and lignocaine infusion ten minutes later. When compared with group 3 hearts, no difference was found between the two groups during the first ten minutes (contusion alone). Two minutes after the contusion, dP/dt_{max} was decreased by 40 ± 3% in group 4 (Figure 5). However, after the initiation of lignocaine infusion, the values for DP, dP/dt_{max} and dP/dt_{min} differed markedly between the

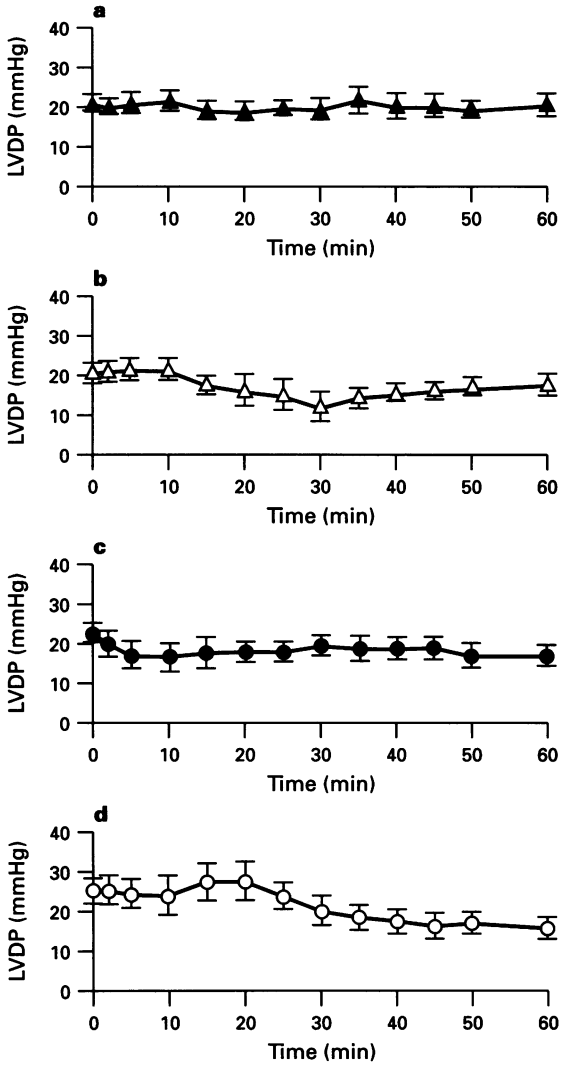

Figure 2 Evolution of left ventricle diastolic pressure (LVDP) in the four groups: (a) group 1 = control (▲); (b) group 2 = lignocaine (△); (c) group 3 = contusion (●); (d) group 4 = contusion + lignocaine (○). Data are displayed as the mean ± s.e. mean.

Table 1 Basal values in the four groups

	Group 1 (*Control*) ($n=6$)	*Group 2* (*Lignocaine*) ($n=7$)	*Group 3* (*Contusion*) ($n=9$)	*Group 4* (*Contusion + lignocaine*) ($n=8$)
Rabbit weight (g)	1960 ± 24	1870 ± 28	1990 ± 33	1980 ± 55
Heart weight (g)	4.9 ± 0.2	5.3 ± 0.2	5.7 ± 0.2	5.2 ± 0.2
Delivered energy (mJ)			431.7 ± 43	358.5 ± 48
% decrease in dP/dt_{max} 2 min after the blow			40 ± 4%	40 ± 3%
		At control time		
LVEDP (mmHg)	20.2 ± 1.3	20.5 ± 1.7	22.7 ± 1.4	24.4 ± 2.3
DP (mmHg)	51.1 ± 3.2	49.0 ± 2.0	54.4 ± 3.5	54.3 ± 3.2
CPP (mmHg)	41.8 ± 3.1	38.2 ± 1.7	40.5 ± 2.7	45.3 ± 3.5
dP/dt_{max} (mmHg s^{-1})	1287 ± 62	1274 ± 84	1327 ± 84	1450 ± 70
dP/dt_{min} (mmHg s^{-1})	998 ± 100	908 ± 88	858 ± 87	1062 ± 71

Data shown are means ± s.e.mean. For key to abbreviations used see text.

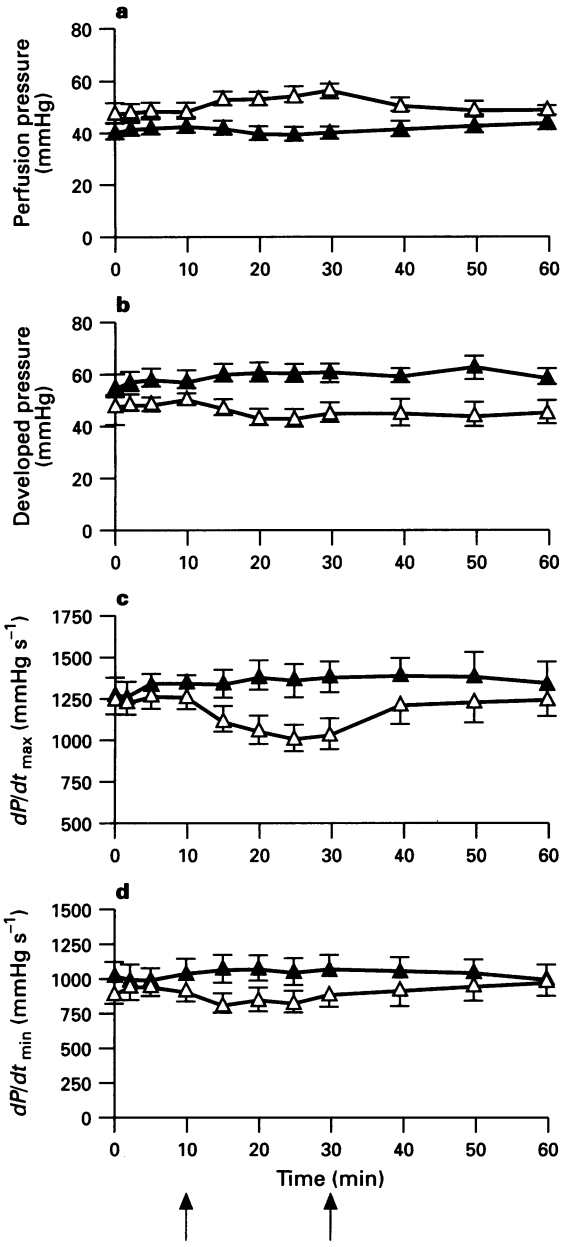

Figure 3 Changes in (a) coronary perfusion pressure, (b) developed pressure, (c) maximum and (d) minimum values of the first derivative of the pressure (dP/dt_{max} and dP/dt_{min}), in group 1 = control (▲) and group 2 = lignocaine (△). Data are shown as the mean ± s.e. mean. The arrows show the start and finish of the lignocaine infusion. dP/dt_{max} and dP/dt_{min} significantly decreased with lignocaine infusion.

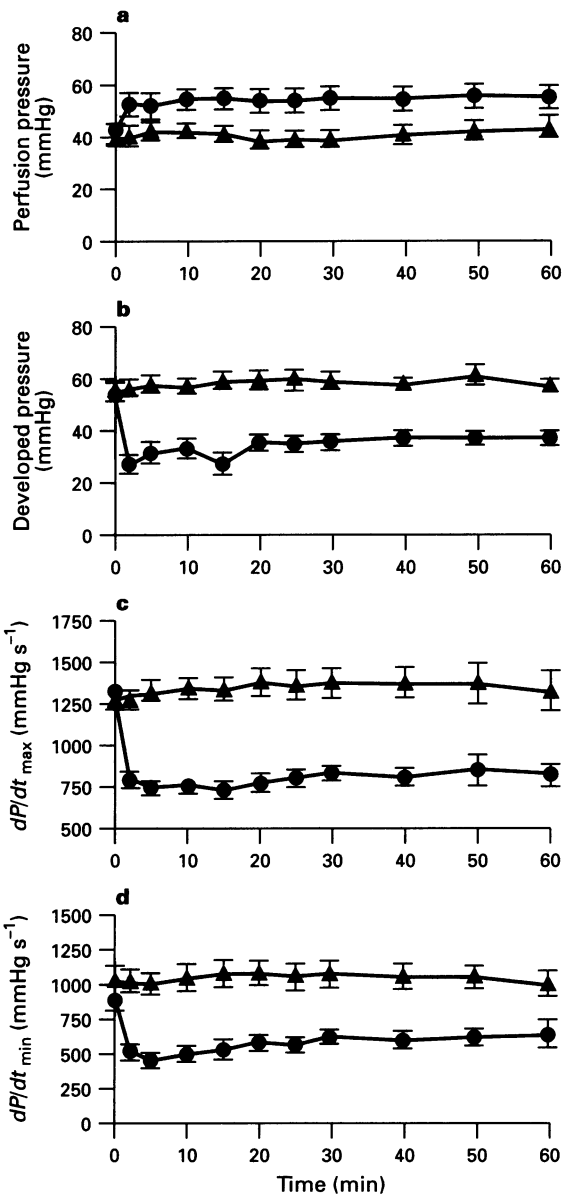

Figure 4 Changes in (a) coronary perfusion pressure, (b) developed pressure, (c) maximum and (d) minimum values of the first derivative of the pressure (dP/dt_{max} and dP/dt_{min}), in group 1 = control (▲) and group 3 = contusion (●). Data are the mean ± s.e. mean. Developed pressure, dP/dt_{max} and dP/dt_{min} significantly decreased with the contusion.

two groups. These parameters returned to their basal values in group 4, even after the cessation of lignocaine infusion. The following parameters were significantly higher in the lignocaine group compared to the contusion group: DP at $t30$, $t40$, and $t50$, dP/dt_{max} at $t20$, $t30$, $t40$, $t50$ and $t60$ and dP/dt_{min} at $t30$, $t40$, $t50$ and $t60$. LVDP did not change. There was a significant increase in CPP with time in both groups but no difference was found between groups.

Discussion

The purpose of this study, done in isolated heart preparations, was to study the effects of lignocaine on the global haemodynamic changes induced by a blunt cardiac trauma. First, it should be pointed out that the animal models of published data exhibit marked differences in terms of methodology, and therefore the results of these studies must be interpreted within the limits of the models used (Liedtke *et al.*, 1980; Desiderio, 1986; Baxter *et al.*, 1988). These studies showed a decrease in myocardial contractile force but it seems difficult to attribute the muscular dysfunction to an impairment in oxygen delivery to cardiac cells from coronary bed or to a direct cell lesion or to both (Baxter *et al.*, 1988).

We used the global contusion model described by Baxter *et al.*, (1988), but with a constant flow, i.e. with a constant oxygen, nutrients and lignocaine inflow. Above all, it must be emphasized that we used realistic lignocaine concentrations. Even corrected for free drug concentration which is considered as the sole fraction crossing the capillary wall, the first infusion (15 μM) was at the upper limit of therapeutic concentrations and the second infusion (30 μM) was at the lower limit of toxic concentrations (Tucker and Mather, 1979).

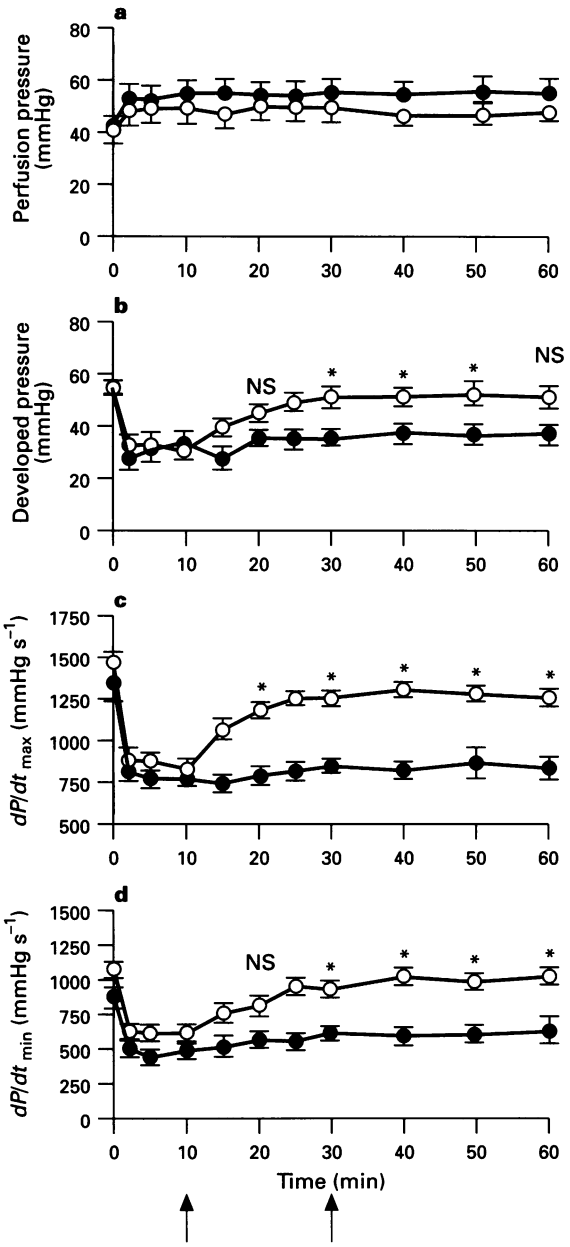

Figure 5 Changes in (a) coronary perfusion pressure, (b) developed pressure, (c) maximum and (d) minimum values of the first derivative of the pressure (dP/dt_{max} and dP/dt_{min}), in group 3 = contusion (●) and group 4 = contusion + lignocaine (○). Data are the mean ± s.e. mean. Coronary perfusion pressure significantly increased after the blow, whereas developed pressure, dP/dt_{max} and dP/dt_{min} significantly decreased after contusion. Lignocaine was infused between 10 and 30 min after the contusion (arrows). Developed pressure, dP/dt_{max} and dP/dt_{min} significantly increased with lignocaine infusion. These parameters remained significantly increased in group 4 (lignocaine + contusion) as compared with group 3 (contusion alone), even after the lignocaine infusion had ceased; $^*P<0.05$; NS, not significant.

Effect of lignocaine

Lignocaine has been shown to exert a coronary vasodilator effect (Marzilli *et al.*, 1979; Gee *et al.*, 1990; Perlmutter *et al.*, 1990) and to depress contractility (Lynch, 1986; Pitkanen *et al.*, 1992). In accordance with these previous observations, we observed a moderate but significant decrease in both dP/dt_{max} and dP/dt_{min}. Several phenomena have been advocated to explain this fall in contractility: alteration of Ca^{2+} release by the sarcoplasmic reticulum (Lynch, 1986; Wilson *et al.*, 1993) or impaired oxygen consumption (Löfström, 1992; Wilson *et al.*, 1993). However, the latter phenomenon has been observed only at concentrations 10 to 100 times higher than the therapeutic concentrations. On the other hand, in the present experiment lignocaine did not induce a decrease in total coronary perfusion pressure (CPP), but rather induced a slight, non-significant increase in CPP. However, lignocaine has been shown to exert either a constrictor or dilator effect on peripheral vessels depending on blood concentration and on the presence or absence of a sympathetic tone (Jorfeldt *et al.*, 1970; Löfström, 1992). Several experiments have shown that high, supratherapeutic doses of lignocaine may increase coronary blood flow (Marzilli *et al.*, 1979; Gee *et al.*, 1990). However, it is possible that the observed increase in coronary blood flow may be the result of a decrease in mean transmural pressure due to asystole observed with the high concentrations used by these authors, or to a combined decrease in systemic pressure and heart rate. Thus, the effect of lignocaine on the coronary vasculature needs to be clarified, although an effect of lignocaine on the coronary vascular tone does not appear to be the primary effect involved in the therapeutic action of lignocaine in myocardial contusion (see below).

Effect of contusion

After the blow, we observed a decrease in contractility attested by the parallel decrease in dP/dt_{max}, dP/dt_{min} and DP. This decrease was maximal at once and remained constant throughout the study period (Figure 4). At this point in the discussion, it should be noted that LVDP did not increase (Figure 1) and that only a slight, non-significant increase in CPP was observed (Figure 4).

The decrease in contractility may be explained by direct damage to the myocardial cells or by a decrease in oxygen and nutrient supply to these cells due to vascular injury, or to both. By producing a global blunt trauma to a rat isolated heart preparation, Baxter *et al.*, (1988) described an increase in coronary resistance following the trauma but they attributed the decrease in contractility to a direct cellular effect. In an anaesthetized pig preparation with trauma localised to the area supplied by the anterior descending coronary artery, Liedtke *et al.* (1980) showed that contusion was followed by a decrease in endocardial blood flow in the injured region of the heart, with an increase in the corresponding pericardial flow and a global increase in coronary blood flow in the non-traumatised parts of the heart. In man, direct injuries to coronary vessels have been described (Malangoni *et al.*, 1992), and the involvement of the coronary vascular bed in the patho-physiology of myocardial contusion may be invoked (Jackimczyk, 1993). However, it is not clear if a decrease in endocardial perfusion initiates the fall in contractility observed in severe myocardial contusion, or if the direct muscular cell injury is the instigating cause of dysfunction. However, changes in coronary perfusion pattern in isolated heart preparations are likely to be due to direct cellular injury: Baxter *et al.* (1988) observed only a slight increase in global vascular resistances and we did not observe any statistically significant increase in CPP. Also, in their rat preparation, Baxter *et al.* (1988) observed an important cellular enzyme release (CPK and LDH) 20 min after the blow (they did not measure any enzyme concentration in the outflow perfusate before that time). These authors concluded that this observation was the consequence of immediate cellular damage, rather than the result of ischaemia because any release produced by ischaemia would have appeared 30 min after the onset of ischaemia. Another convincing argument lies in the fact that in these injured hearts we did not observe any increase in diastolic pressure ('contracture' phenomenon) usually observed in the case of ischaemia (Butwell *et al.*, 1993). Thus, all these facts seem to favour the cellular hypothesis rather than the vascular hypothesis.

Effect of lignocaine on injured hearts

We infused lignocaine in eight rabbit hearts. This lignocaine infusion was begun ten minutes after injury as a curative

treatment. In a similar way, lignocaine infusion was stopped 20 min after its initiation and we continued to measure the haemodynamic variables for a further 20 min i.e. after almost complete myocardial washout (Mazoit *et al.*, 1990). Lignocaine markedly improved contractility rapidly after its infusion, and this effect persisted after the end of infusion as though lignocaine was able to break a vicious circle or to re-establish an impaired function. No effect of lignocaine was observed on CPP (Figure 5) which demonstrates that lignocaine does not exert its beneficial effect by improving coronary perfusion. In point of fact, our model cannot differentiate between endocardial and epicardial flows but it would be unlikely that a change in transmural flow ratio would occur without any change in the global flow pattern.

Thus, it appears that lignocaine improves contractility by a direct cellular mechanism. Lignocaine has not been studied (to our knowledge) in myocardial contusion and we must infer a possible mechanism from studies done on other models. Although contusion markedly differs from ischaemia or hypoxia and reperfusion syndrome, it is interesting to note that lignocaine (at concentrations much higher than those used in the present study) has been shown to exert a protective effect against the degradation of myocardial function induced by ischaemia (Butwell *et al.*, 1993), hypoxia (Takeo *et al.*, 1989), reactive oxygen radicals infusion (Hara *et al.*, 1993) or reperfusion after ischaemia or hypoxia-reperfusion experiments (Tozaki *et al.*, 1988; Takeo *et al.*, 1989). Three main mechanisms have been proposed to explain the effect of lignocaine in these conditions (Takeo *et al.*, 1989; Butwell *et al.*, 1993): (1) the conservation of high-energy phosphates, (2) the decrease of transmembrane flux of sodium and calcium in cardiac cells and (3) the attenuation of myocardial acidosis, the latter effect being related to the first two factors. It is impossible in our experiments to differentiate between these possible explanations. However, it is important to note that lignocaine improves myocardial developed pressure, thus increasing the energy expenditure due to mechanical activity (considering equal efficiency).

In conclusion, this study demonstrates that, within the limits of our experiments, lignocaine may have a beneficial effect on contractility after myocardial contusion. Moreover, this effect was obtained at low therapeutic concentrations and persists even after the cessation of lignocaine infusion. Further studies are needed to confirm these results and elucidate the mechanisms involved. Nevertheless, after these preliminary experiments in the isolated organ, the effect of lignocaine must be tested in the intact animal and thereafter in clinical situations.

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