Haemodynamic alterations in anaesthetized and acutely intoxicated newborn piglets

*Cara J. Chandler, *†Bill Y. Ong, ¹*‡Daniel S. Sitar

Departments of *Pharmacology & Therapeutics, †Anaesthesia and ‡Internal Medicine, Faculty of Medicine, University of Manitoba, Winnipeg, Canada, R3E 0W3

- 1 We investigated the haemodynamic alterations in 2-day old anaesthetized piglets after acute ethanol intoxication using the microsphere technique.
- 2 After ethanol infusion, mean arterial blood pressure (MABP) decreased by 6%, cardiac output (CO) decreased by 26%, heart rate (HR) increased by 20% and systemic vascular resistance (SVR) increased by 36%.
- 3 Arterial perfusion to the kidneys, gastrointestinal (GI) organs and carcass decreased by 39%, 34% and 26%, respectively.
- 4 In piglets pretreated with 4-methylpyrazole (4-MP), an alcohol dehydrogenase inhibitor, the decrease in MABP and increase in HR were not observed after ethanol infusion, but the reduction in CO and increase in SVR were maintained.
- 5 Arterial blood flow to the GI organs and carcass, but not the kidneys, remained at significantly reduced levels.
- 6 These observations indicate that ethanol can adversely affect CO and arterial perfusion to GI and musculoskeletal structures while metabolites of ethanol, such as acetaldehyde, affect MABP and HR. Therefore, the clinical effects observed after acute ethanol intoxication in neonates may vary with their rate of ethanol metabolism.

Introduction

Although the adverse effects of chronic ethanol exposure on the foetus (Jones *et al.*, 1974; Hanson *et al.*, 1976) are well characterized, the effects of acute ethanol intoxication on the newborn are still unclear. Previous studies in foetal and newborn lambs, as far as mean arterial blood pressure (MABP) and heart rate (HR) are concerned, have produced conflicting results (Mann *et al.*, 1975; Ayromloo *et al.*, 1979; Cook *et al.*, 1981; Cumming *et al.*, 1985). Previously, we have found that newborn piglets have rates of ethanol metabolism close to those reported for human neonates ($2.0 \pm 0.2 \text{ mmol l}^{-1} \text{ h}^{-1}$), and that acutely intoxicated piglets develop significant hypotension and tachycardia which can be reversed by blocking ethanol metabolism with 4-methylpyrazole (4-MP) (Chandler *et al.*, 1989). The present series of experiments was undertaken to determine cardiac output (CO), systemic vascular resistance (SVR) and regional blood flow distribution in acutely intoxicated newborn piglets and to assess the effects of blocking ethanol metabolism with 4-MP.

Methods

Surgical preparation

Healthy farm-bred two-day old Camborough piglets with a mean weight of $1.34 \pm 0.06 \text{ kg}$ were the subjects of this study. All incisions were infiltrated with 1% lignocaine hydrochloride. Anaesthesia was induced with 1% halothane and tracheostomies were performed. After tracheostomies, piglets were paralyzed with 0.3 mg kg^{-1} (+)-tubocurarine, halothane was discontinued and anaesthesia was maintained with 70% nitrous oxide in oxygen. Tidal volume and ventilation rate were adjusted via a Harvard Apparatus respirator to maintain a PaCO_2 range of 35 to 45 mmHg. Polyethylene catheters (PE-60) were placed in the femoral artery to monitor MABP and

to collect blood ethanol, arterial blood gas and microsphere reference samples and in the femoral vein for ethanol or 5% dextrose in water infusion. Additional catheters (PE-100) were placed into the left ventricle via the left carotid artery for the injection of microspheres and into the left jugular vein for central venous pressure (CVP) measurements. Placement of the catheter in the left ventricle was performed by following the ventricular pressure tracing. The location of all catheters was verified at autopsy. Body temperature was maintained constant with a servo-controlled overhead heater at 38°C. All piglets were allowed to rest for 2 h after surgical procedures and before experiments were started to insure stability after the surgical stress and to allow for recovery from the single dose of (+)-tubocurarine.

Series 1 experiments

The aim of this study was to examine the haemodynamic effects of acute ethanol intoxication. Piglets were randomly assigned into one of two groups. Six piglets (E) received ethanol, 1.4 g kg^{-1} , over 30 min while 6 piglets (C) received an equivalent volume of dextrose solution. Blood flow to the various regions was assessed by the microsphere technique before the ethanol or dextrose infusion and 90 min after the end of the infusion. MABP and HR were monitored continuously and arterial blood gases, haematocrit and CVP measurements were carried out before each microsphere measurement. Arterial blood samples (0.5 ml) were taken immediately prior to the last microsphere measurement to determine plasma ethanol concentrations.

Series 2 experiments

The aim of this study was to determine the effects of blocking ethanol metabolism with 4-MP on ethanol-induced haemodynamic changes. Piglets were randomly assigned into one of two groups. Four piglets (CMP) received 4-MP, 50 mg kg^{-1} , intravenously over a 15 min infusion interval prior to dextrose infusion while six piglets (EMP) received 4-MP prior to ethanol infusion. Blood flow to the various regions was assessed by the microsphere technique before the 4-MP infusion, 15 min after the end of the 4-MP infusion and 90 min after the

¹ Author for correspondence at: Clinical Pharmacology Section, University of Manitoba, 770 Bannatyne Avenue, Winnipeg, Manitoba R3E 0W3, Canada.

end of the dextrose or ethanol infusion. MABP and HR were monitored continuously while arterial blood gases, haematocrit and CVP determinations were made prior to each microsphere measurement. Arterial blood samples (0.5 ml) were taken at 5, 30 and 90 min after the end of the dextrose or ethanol infusion to determine plasma ethanol concentrations.

Microsphere technique

Microspheres, $15 \pm 5 \mu\text{m}$ diameter, were labelled with ^{85}Sr , ^{141}Ce or ^{51}Cr (3M Company, St. Paul, Minnesota, U.S.A.). Approximately 1×10^6 microspheres were suspended in 1 ml of 10% dextran and 0.02% Tween 80 and injected into the left ventricle. The catheter was then flushed with 2 ml of 0.9% saline. A reference sample of blood from the abdominal aorta was collected continuously with a pump for 2 min beginning 10 s prior to the microsphere injection at a constant withdrawal rate of 0.97 ml min^{-1} . At the end of the experiment, each anaesthetized animal was killed by an injection of saturated KCl into the left ventricle.

The brain was separated from the spinal cord at the level of the first cervical vertebra and divided into left and right hemispheres. The brain was then dissected into regions representing the cerebellum, cortex, basal ganglia and brainstem. All sections were weighed and placed in counting vials to heights of 1 cm.

The heart, stomach and right and left kidneys were removed, weighed and placed in counting vials. The small and large bowel, liver and the remaining parts of the piglet (carcass) were weighed separately and individually incinerated at 300°C for 72 h. After obtaining the dry weight of the tissues, the organs were ground into a fine powder with a mortar and pestle and aliquots of the resulting ash were placed in counting vials to a height of 1 cm.

Radioactivity from all regions and reference samples was measured by an automatic gamma counting system (1185 Series, Nuclear-Chicago). Blood flow to the various regions was calculated according to the equation: organ flow = (c.p.m. organ/c.p.m. reference sample) $\times$ rate of withdrawal of reference sample. All blood and tissue samples contained at least 400 microspheres. Adequate mixing of the microspheres was confirmed by comparing blood flow to the left brainstem, basal ganglia, cortex, cerebellum and kidney with the respective blood flow to corresponding structures on the right side.

Ethanol analysis

Arterial blood samples were placed in tubes containing potassium oxalate and sodium fluoride, mixed and placed on ice. Within 2 h, the samples were centrifuged for 2 min in a Fisher microcentrifuge (model 235A) and the plasma separated and stored at -20°C .

Plasma ethanol concentrations were determined by gas-liquid chromatography on a Hewlett Packard model 402 instrument using a flame ionization detector and a Poropak Q/R column (Cumming *et al.*, 1984). Operating parameters included a column and injector port temperature of 150°C and a detector temperature of 250°C . Nitrogen was used as the carrier gas and propranol-1 (0.02% v/v) as the internal standard.

Data analysis

The calibration curve for ethanol quantitation was determined by the least squares linear regression analysis of the peak height ratio of ethanol:propranol-1 to assess the goodness of fit (Goldstein, 1964).

Analysis of variance for repeated measurements was used to detect statistical significance. Multiple group comparisons were made with Duncan's multiple range test with $P < 0.05$ indicating statistical significance. All values are expressed as means $\pm$ s.e.mean.

Results

Arterial blood gases, pH and haematocrit values for control (C) and ethanol-treated (E) piglets are shown in Table 1. Similar data for the control 4-methylpyrazole-treated (CMP) and 4-methylpyrazole and ethanol-infused (EMP) piglets are shown in Table 2. There was no significant difference in any of these parameters between C and E or CMP and EMP piglets. In addition, 4-MP pretreatment did not affect arterial blood gases, pH or haematocrit.

Baseline MABP, HR, CO and SVR values for the four groups of piglets are summarized in Table 3. Changes in these parameters 90 min after dextrose or ethanol infusion,

Table 1 Arterial blood gases, pH and haematocrit (HCT) changes in Series 1 piglets

Parameter	Group	Pre-infusion	Post-infusion
PO_2 (mmHg)	C	107 ± 7	106 ± 6
	E	117 ± 6	114 ± 6
PCO_2 (mmHg)	C	37 ± 1	38 ± 1
	E	37 ± 1	37 ± 1
pH	C	7.41 ± 0.03	7.40 ± 0.02
	E	7.42 ± 0.02	7.40 ± 0.03
HCT	C	29 ± 1	29 ± 1
	E	28 ± 1	29 ± 1

Values are means $\pm$ s.e.mean for 6 piglets. Control (C) piglets received dextrose while treated (E) piglets received ethanol. Pre-infusion before dextrose or ethanol infusion and post-infusion is 90 min after the end of dextrose or ethanol infusion.

Table 2 Arterial blood gases, pH and haematocrit (HCT) values in Series 2 piglets

Parameter	Group	Pre 4-MP	Post 4-MP	Post-infusion
PO_2 (mmHg)	CMP	130 ± 9	135 ± 10	130 ± 12
	EMP	120 ± 10	124 ± 10	122 ± 9
PCO_2 (mmHg)	CMP	38 ± 1	39 ± 1	37 ± 1
	EMP	37 ± 1	39 ± 1	37 ± 1
pH	CMP	7.34 ± 0.03	7.30 ± 0.04	7.33 ± 0.01
	EMP	7.34 ± 0.01	7.33 ± 0.01	7.33 ± 0.01
HCT	CMP	28 ± 1	28 ± 1	29 ± 1
	EMP	28 ± 1	28 ± 1	28 ± 1

Values are means $\pm$ s.e.mean. Four control (CMP) piglets received 4-methylpyrazole (4-MP) prior to 5% dextrose in water infusion while six treated (EMP) piglets received 4-MP prior to ethanol infusion. 'Pre 4-MP' is before 4-MP infusion, 'Post 4-MP' is after 4-MP infusion and 'Post-infusion' is 90 min after the end of dextrose or ethanol infusion.

Table 3 Baseline mean arterial blood pressure, heart rate, cardiac output and systemic vascular resistance values in Series 1 and 2 piglets

Group	MABP	HR	CO	SVR
C	86 ± 4	225 ± 10	20 ± 2	3.5 ± 0.3
E	95 ± 7	196 ± 6	27 ± 3	3.4 ± 0.4
CMP	71 ± 2	213 ± 9	24 ± 4	3.0 ± 0.3
EMP	81 ± 5	197 ± 14	25 ± 2	3.2 ± 0.3

Values are means $\pm$ s.e.mean. There are six animals per group, except for CMP piglets where only four animals were studied. Mean arterial blood pressure (MABP) is expressed as mmHg, heart rate (HR) as beats min^{-1} , cardiac output (CO) as $\text{ml } 100 \text{ g}^{-1} \text{ min}^{-1}$ and systemic vascular resistance (SVR) as $\text{mmHg ml}^{-1} 100 \text{ g}^{-1} \text{ min}^{-1}$. For other abbreviations, see text.

Figure 1 Changes in mean arterial blood pressure (MABP), heart rate (HR), cardiac output (CO) and systemic vascular resistance (SVR). Each column represents the value 90 min after dextrose or ethanol infusion as a percentage of its preinfusion value. Series 1 control piglets (C), open columns; Series 1 ethanol-treated piglets (E), cross hatched columns; Series 2 control 4-methylpyrazole-treated piglets (CMP) solid columns; Series 2 ethanol-infused 4-MP-treated piglets (EMP) hatched columns. Values are means $\pm$ s.e.mean. * $P < 0.05$ and ** $P < 0.01$ compared to preinfusion value. There are six animals per group, except for CMP piglets, where only four animals were studied.

Figure 2 Changes in regional blood flow. Each column represents arterial perfusion 90 min after dextrose or ethanol infusion as a percentage of its preinfusion value. Series 1 C piglets, open columns; Series 1 E piglets, cross-hatched columns; Series 2 CMP piglets, solid columns; Series 2 EMP piglets, hatched columns. Values are means with s.e.mean shown by vertical bars. ** $P < 0.01$ compared to preinfusion value. There are six animals per group, except for CMP piglets, where only four animals were studied.

Table 5 Haemodynamic parameters in Series 2 piglets before (Pre 4-MP) and after (Post 4-MP) 4-methylpyrazole infusion

Parameter	Group	Pre 4-MP	Post 4-MP
MABP	CMP	72 $\pm$ 3	71 $\pm$ 2
	EMP	82 $\pm$ 5	81 $\pm$ 5
HR	CMP	208 $\pm$ 3	213 $\pm$ 9
	EMP	200 $\pm$ 12	197 $\pm$ 14
CO	CMP	23 $\pm$ 3	24 $\pm$ 4
	EMP	25 $\pm$ 2	25 $\pm$ 2
SVR	CMP	3.3 $\pm$ 0.3	3.0 $\pm$ 0.3
	EMP	3.3 $\pm$ 0.4	3.2 $\pm$ 0.3

Values are means $\pm$ s.e.mean. Four animals were studied in the CMP group and six in the EMP group. Mean arterial blood pressure (MABP) is expressed in mmHg, heart rate (HR) in beats min^{-1} , cardiac output (CO) in $\text{ml } 100 \text{ g}^{-1} \text{ min}^{-1}$ and systemic vascular resistance (SVR) in $\text{mmHg } 100 \text{ g}^{-1} \text{ min}^{-1}$. For other abbreviations, see text.

expressed as a percentage of the value immediately prior to dextrose or ethanol infusion, are illustrated in Figure 1. After the end of the ethanol infusion, a 6% decrease in MABP ($P < 0.05$) and 20% increase in HR ($P < 0.01$) were observed in E piglets while no change was seen in EMP piglets receiving 4-MP prior to ethanol infusion. In C and CMP piglets, MABP and HR values after dextrose infusion were not different from values obtained prior to dextrose infusion. There was a reduction in CO ($P < 0.05$) and an increase in SVR ($P < 0.05$) after ethanol infusion in E and EMP piglets. In C and CMP piglets, CO and SVR values after dextrose infusion were not different from values obtained prior to dextrose infusion.

Baseline CVP values were 0.8 ± 0.4 , 0.8 ± 0.4 , 0.8 ± 0.2 and $0.8 \pm 0.2 \text{ cmH}_2\text{O}$ in C, E, CMP and EMP piglets, respectively. After dextrose or ethanol infusion, the corresponding values were 0.7 ± 0.4 , 0.6 ± 0.3 , 0.6 ± 0.3 and $0.6 \pm 0.3 \text{ cmH}_2\text{O}$.

Figure 3 Changes in regional blood flow after 4-methylpyrazole (4-MP) infusion. Open columns, CMP piglets; hatched columns, EMP piglets. Values are means with s.e.mean shown by vertical bars. Four animals were studied in the CMP group and six in the EMP group.

Table 4 Baseline arterial blood flow ($\text{ml } 100 \text{ g}^{-1} \text{ min}^{-1}$) in Series 1 and 2 piglets

Group	Brain	Heart	Liver	Kidneys	GI	Carcass
C	53 $\pm$ 8	184 $\pm$ 36	53 $\pm$ 11	198 $\pm$ 25	62 $\pm$ 12	11 $\pm$ 1
E	59 $\pm$ 6	186 $\pm$ 33	77 $\pm$ 21	188 $\pm$ 18	93 $\pm$ 32	16 $\pm$ 2
CMP	76 $\pm$ 18	218 $\pm$ 31	61 $\pm$ 13	175 $\pm$ 25	61 $\pm$ 9	14 $\pm$ 3
EMP	68 $\pm$ 7	210 $\pm$ 35	44 $\pm$ 9	186 $\pm$ 17	73 $\pm$ 8	15 $\pm$ 1

Values are means $\pm$ s.e.mean. There are six animals per group, except for CMP piglets, where only four animals were studied. For abbreviations, see text.

Table 6 Regional cerebral blood flow (ml 100 g⁻¹ min⁻¹) in Series 1 and 2 piglets before (Pre) and 90 min after (Post) the end of dextrose or ethanol infusion

Region	Group	Pre	Post
Brainstem	C	54 ± 8	62 ± 6
	E	60 ± 7	58 ± 3
	CMP	76 ± 22	80 ± 16
	EMP	76 ± 3	74 ± 8
Cerebellum	C	60 ± 4	58 ± 3
	E	64 ± 3	64 ± 9
	CMP	81 ± 19	80 ± 8
	EMP	67 ± 6	68 ± 11
Basal ganglia	C	79 ± 8	75 ± 7
	E	85 ± 9	86 ± 9
	CMP	117 ± 30	116 ± 21
	EMP	101 ± 7	98 ± 12
Cortex	C	53 ± 6	51 ± 7
	E	64 ± 5	56 ± 8
	CMP	76 ± 18	67 ± 9
	EMP	68 ± 8	68 ± 7

Values are means ± s.e.mean. There are six animals per group, except for CMP piglets, where only four animals were studied. In series 1, control (C) piglets received dextrose infusion and treated (E) piglets received ethanol infusion. In series 2, control (CMP) piglets received 4-methylpyrazole (4-MP) prior to the dextrose infusion, and treated piglets (EMP) received an ethanol infusion after pretreatment with 4-MP.

There was no significant difference in CVP between piglet groups or after dextrose or ethanol infusion.

Baseline regional blood flow data are presented in Table 4. Changes in these values 90 min after dextrose or ethanol infusion, expressed as a percentage of the value immediately prior to dextrose or ethanol infusion, are illustrated in Figure 2. Blood flow to all regions tested remained constant in C and CMP piglets. There were decreases in renal, GI and carcass blood flow ($P < 0.01$) after ethanol administration in E piglets while only GI and carcass blood flow reductions ($P < 0.01$) were observed in EMP piglets.

Plasma ethanol concentrations were higher in piglets receiving 4-MP prior to ethanol infusion compared to those receiving ethanol alone ($P < 0.05$). Ninety min after the end of the ethanol infusion, plasma ethanol concentration was 36.3 ± 3.9 mmol l⁻¹ in EMP piglets and 31.1 ± 2.2 mmol l⁻¹ in E piglets. Plasma ethanol concentration remained steady over the study duration in EMP piglets, showing that 4-MP effectively blocked ethanol metabolism for the duration of the study.

There were no changes in MABP, HR, CO or SVR following 4-MP infusion in both CMP and EMP piglets (Table 5). Similarly, regional blood flow was not altered in these piglets after 4-MP infusion (Figure 3).

Blood flow to the brainstem, cerebellum, basal ganglia and cortex are shown in Table 6. Blood flow to these brain regions remained constant in all four groups with the basal ganglia receiving the most perfusion within groups.

Discussion

The major findings of these studies are the reduced cardiac output (CO) and altered regional blood flow observed after acute ethanol intoxication in the newborn piglet and the prevention of hypotension and tachycardia with 4-MP treatment prior to ethanol administration.

In our study, CO significantly decreased 26% from baseline values 90 min after the end of the ethanol infusion. Normal CO depends on both venous return and myocardial contractility. The maintenance of CVP readings does not indicate any pooling of blood in the peripheral compartments. In addition, the constancy of haematocrit values suggests that there is no significant alteration of plasma volume due to any diuretic effect of ethanol. These data strongly imply that the reduction

in CO is the direct result of impaired myocardial contractility by ethanol.

It is recognized that acute ethanol intoxication may depress cardiac performance in adult animals (Horwitz & Atkins, 1974; Stratton *et al.*, 1981) and man (Lang *et al.*, 1985; Kelbaek *et al.*, 1985). In foetal lambs, Kirkpatrick *et al.* (1976) observed a significant depression in the extent and velocity of left ventricular myocardial fibre shortening at blood ethanol concentrations of 23.9 and 45.7 mmol l⁻¹. These indices of cardiac contractility were depressed in the absence of changes in end diastolic diameter, left atrial pressure and systemic arterial pressure. In foetal lambs, Urfer *et al.* (1984) reported a significant difference in the pre-ejection period to ejection time ratio observed before ethanol infusion to that seen 15 and 30 min after ethanol infusion, at blood ethanol concentrations of about 19.6 mmol l⁻¹. Both studies concluded that myocardial function is compromised with acute ethanol intoxication. Our observation of a 26% decrease in CO after ethanol administration in the neonatal piglet is consistent with the finding in the foetal lamb.

The effects of ethanol on regional blood flow in newborn animals have not been reported previously. In our study, arterial blood flow to the brain, heart and liver was maintained while flow to the kidneys, GI organs and carcass was decreased. The reduction in blood flow to GI organs observed after ethanol administration to the neonate is in contrast to the increase in splanchnic blood flow observed in adult humans (Stein *et al.*, 1963) and animals (Cheung *et al.*, 1975; Shaw *et al.*, 1977; Friedman *et al.*, 1979; Friedman *et al.*, 1981; McKaigney *et al.*, 1986). The differences observed in regional blood flow after ethanol administration may be related to age, species and type of anaesthetic used.

As in our previous studies (Chandler *et al.*, 1989), MABP was significantly decreased and HR increased by 90 min after the end of the ethanol infusion. These haemodynamic alterations suggest an adverse cardiovascular effect of acute ethanol administration. Such adverse effects are consistent with previous reports of human neonatal depression (Peden *et al.*, 1973; Cook *et al.*, 1975) and neonatal death (Jung *et al.*, 1980) after ethanol intoxication.

Total and regional CBF were maintained after ethanol intoxication. These observations confirm our previous reports of the maintenance of CBF and CBF autoregulation in intoxicated newborn piglets (MacIntyre *et al.*, 1987). Maintenance of CBF has also been observed by Mann *et al.* (1975) in foetal lambs at blood ethanol concentrations up to 47.8 mmol l⁻¹.

4-MP successfully blocked ethanol metabolism in newborn piglets. Steady-state plasma ethanol concentrations were achieved over the duration of our study with a dose of 50 mg kg⁻¹ of 4-MP without any significant haemodynamic responses or changes in arterial blood gases. These findings are consistent with studies on 4-MP in rats by Hellstrom & Tottmar (1982).

In piglets given 4-MP before ethanol infusion, the decrease in CO seen after ethanol infusion alone was still observed. Therefore, ethanol itself, rather than its metabolites, may be the major cause of the reduction in CO observed with acute ethanol intoxication. However, the decrease in MABP seen after ethanol administration alone was not observed in those piglets pretreated with 4-MP. In adult rats, Hellstrom & Tottmar (1982) also observed that 4-MP given prior to ethanol administration prevented the decrease in MABP observed with ethanol treatment. This suggests that the reduction in MABP could be due to a metabolite such as acetaldehyde. This is consistent with other reports on the vasodilator effects of acetaldehyde (Altura *et al.*, 1978; Hellstrom & Tottmar, 1982). Inhibition of alcohol dehydrogenase activity with 4-MP and consequent blockade of acetaldehyde production would abolish the hypotension observed after ethanol treatment.

4-MP prevented the decrease in renal flow observed after ethanol treatment alone. However, the reduction in GI blood flow was not abolished by 4-MP pretreatment. The preser-

vation of renal blood flow may be a beneficial effect of maintaining arterial blood pressure at baseline level.

Previous studies in foetal lambs have shown transient tachycardia but no consistent blood pressure changes (Ayromlooi *et al.*, 1979; Cook *et al.*, 1981). Those results may be accounted for by the significantly lower ethanol metabolic rate in foetal and newborn lambs (Cumming *et al.*, 1985) compared to newborn humans (Wagner *et al.*, 1970; Fuchs & Fuchs, 1981) and piglets (Chandler *et al.*, 1989).

In conclusion, acute ethanol intoxication caused significant hypotension, tachycardia, decreased CO, elevated SVR and altered regional blood flows in neonatal piglets. 4-MP

pretreatment prevented the reduction in MABP and the increase in HR but did not affect the CO decrease or SVR increase observed after ethanol alone. Ethanol is a cardiac depressant while its metabolites, such as acetaldehyde, probably play a major role in the hypotension and tachycardia observed after ethanol intoxication.

This research was supported by the Manitoba Heart Foundation and the Medical Research Council of Canada. C.J.C. was supported by a Medical Research Council Studentship and is at present the recipient of a Heart and Stroke Foundation of Canada Medical Scientist Fellowship.

References

- ALTURA, B.M., CARELLA, A. & ALTURA, B.T. (1978). Acetaldehyde on vascular smooth muscle: possible role in vasodilator action of ethanol. *Eur. J. Pharmacol.*, **52**, 73–83.
- AYROMLOOI, J., TOBIAS, M., BERG, P. & DESIDERIO, D. (1979). Effects of ethanol on the circulation and acid-base balance of pregnant sheep. *Obstet. Gynecol.*, **54**, 624–630.
- CHANDLER, C.J., ONG, B.Y. & SITAR, D.S. (1989). Kinetic disposition of ethanol in the neonatal piglet and hemodynamic effects in the presence and absence of 4-methylpyrazole. *Toxicol. Appl. Pharmacol.*, **99**, 185–192.
- CHEUNG, L.Y., MOODY, F.G. & REASE, R.S. (1975). Effect of aspirin, bile salt, and ethanol on canine gastric mucosal blood flow. *Surgery*, **77**, 786–792.
- COOK, P.S., ABRAMS, R.M., NOTELOVITZ, M. & FRISINGER, J.E. (1981). Effects of ethyl alcohol on maternal and fetal acid-base balance and cardiovascular status in chronic sheep preparations. *Br. J. Obstet. Gynaecol.*, **88**, 188–194.
- COOK, L.N., SHOTT, R.J. & ANDREWS, B.F. (1975). Acute transplacental ethanol intoxication. *Am. J. Dis. Child.*, **129**, 1075–1076.
- CUMMING, M.E., ONG, B.Y., WADE, J.G. & SITAR, D.S. (1984). Maternal and fetal ethanol pharmacokinetics and cardiovascular responses in near-term pregnant sheep. *Can. J. Physiol. Pharmacol.*, **62**, 1435–1439.
- CUMMING, M.E., ONG, B.Y., WADE, J.G. & SITAR, D.S. (1985). Ethanol disposition in newborn lambs and comparison of alcohol dehydrogenase activity in placenta and maternal sheep, fetal and neonatal lamb liver. *Dev. Pharmacol. Ther.*, **8**, 338–345.
- FRIEDMAN, H.S., NEIL, C. & DOWD, A. (1979). Effects of ethanol on regional blood flow. *Clin. Res.*, **27**, 562 (abstr).
- FRIEDMAN, H.S., LOWERY, R., ARCHER, M. & SCORZA, J. (1981). The effects of ethanol on regional blood flow in awake dogs. *Clin. Res.*, **29**, 650 (abstr).
- FUCHS, A.-R. & FUCHS, F. (1981). Ethanol for prevention of pre-term birth. *Semin. Perinatol.*, **5**, 236–251.
- GOLDSTEIN, A. (1964). *Biostatistics: an Introductory Text*. pp. 63–69. New York: Macmillan.
- HANSON, J.W., JONES, K.L. & SMITH, D.W. (1976). Fetal alcohol syndrome: experience with 41 patients. *J. Am. Med. Assoc.*, **235**, 1458–1460.
- HELLSTROM, E. & TOTTMAR, O. (1982). Acute effects of ethanol and acetaldehyde on blood pressure and heart rate in disulfiram-treated and control rats. *Pharmacol. Biochem. Behav.*, **17**, 1103–1109.
- HORWITZ, L.D. & ATKINS, J.M. (1974). Acute effects of ethanol on left ventricular performance. *Circulation*, **49**, 124–128.
- JONES, K.L., SMITH, D.W., STREISSGUTH, A.P. & MYRIANTHOPOULOS, N.C. (1974). Outcome in offspring of chronic alcoholic women. *Lancet*, **i**, 1076–1078.
- JUNG, A.L., ROAN, Y. & TEMPLE, A.R. (1980). Neonatal death associated with acute transplacental ethanol intoxication. *Am. J. Dis. Child.*, **134**, 419–420.
- KELBAEK, H., GJORUP, T., BRYNJOLF, I., CHRISTENSEN, N.J. & GODTFREDSEN, J. (1985). Acute effects of alcohol on left ventricular function in healthy subjects at rest and during upright exercise. *Am. J. Cardiol.*, **55**, 164–167.
- KIRKPATRICK, S.E., PITLICK, P.T., HIRSCHKLAU, M.J. & FRIEDMAN, W.F. (1976). Acute effects of maternal ethanol infusion on fetal cardiac performance. *Am. J. Obstet. Gynecol.*, **126**, 1034–1037.
- LANG, R.M., BOROW, K.M., NEUMANN, A. & FELDMAN, T. (1985). Adverse cardiac effects of acute alcohol ingestion in young adults. *Ann. Intern. Med.*, **102**, 742–747.
- MACINTYRE, C.J., ONG, B.Y. & SITAR, D.S. (1987). Cerebral blood flow in intoxicated newborn piglets. *Can. J. Physiol. Pharmacol.*, **65**, 92–95.
- MANN, L.I., BHAKTHAVATHSALAN, A., LIU, M. & MAKOWSKI, P. (1975). Effect of alcohol on fetal cerebral function and metabolism. *Am. J. Obstet. Gynecol.*, **122**, 845–851.
- McKAIGNEY, J.P., CARMICHAEL, F.J., SALDIVIA, V., ISREAL, Y. & ORREGO, H. (1986). Role of ethanol metabolism in the ethanol-induced increase in splanchnic circulation. *Am. J. Physiol.*, **250**, G518–G523.
- PEDEN, V.H., SAMMON, T.J. & DOWNEY, D.A. (1973). Intravenously induced infantile intoxication with ethanol. *J. Pediatr.*, **83**, 490–493.
- SHAW, S., HELLER, E.A., FRIEDMAN, H.S., BARAONA, E. & LIEBER, C.S. (1977). Increased hepatic oxygenation following ethanol administration in the baboon. *Proc. Soc. Exp. Biol. Med.*, **156**, 509–513.
- STEIN, S.W., LIEBER, C.S., LEEVY, C.M., CHERRICK, G.R. & ABELMANN, W.H. (1963). The effect of ethanol upon systemic and hepatic blood flow in man. *Am. J. Clin. Nutr.*, **13**, 68–74.
- STRATTON, R., DORMER, K.J. & ZEINER, A.R. (1981). The cardiovascular effects of ethanol and acetaldehyde in exercising dogs. *Alcoholism*, **5**, 56–63.
- URFER, F.N., FOURON, J.C., BARD, H. & DE MUYLDER, X. (1984). Low levels of blood alcohol and fetal myocardial function. *Obstet. Gynecol.*, **63**, 401–404.
- WAGNER, L., WAGNER, G. & GUERRERO, J. (1970). Effect of alcohol on premature newborn infants. *Am. J. Obstet. Gynecol.*, **108**, 308–315.

(Received March 2, 1990

Revised April 30, 1990

Accepted May 2, 1990)