Acute decrease of coronary flow after indomethacin delivery in newborn lambs

Solweig Harling[1], Gylfi Oskarsson [1], Saemundur Gudmundsson[2], Erkki Pesonen[1]

[1] Departments of Paediatrics, University Hospital Lund, Sweden. [2]Departments of Obstetric and Gynaecology, University Hospital Malmoe, Sweden.

Corresponding author: Solweig Harling, Division of Paediatric Cardiology, University Hospital, S-22185, Lund, Sweden.Tel +4646178158, Fax +4646157149. E-mail solweig.harling@med.lu.se

Abstract

Aim: To document the effects of indomethacin on coronary flow.

Methods: We studied nine premature lambs during the first day of life. The gestational age varied between 132 and 134 days (term 145 days) and weight 3.1-4.7 kg. Coronary flow velocities were recorded with an intracoronary Doppler guide wire in the proximal left anterior descending coronary artery. Average peak flow velocity was measured before during and after an intravenous indomethacin injection of 0,2 mg per kilogram of body weight.

Results: Indomethacin increased systemic blood pressure ($p < 0,05$) and rate pressure product ($p<0,05$) indicating that indomethacin increased cardiac workload. Indomethacin decreased coronary average peak flow velocity in all lambs ($p<0.05$). The maximal fall in coronary velocity appeared after 3 (range 1-7) and was regained 10 (range 4-53) minutes after the drug delivery. The maximal reduction of coronary average peak flow velocity was 52 per cent (median 26). The recovery time was directly related to the maximal reduction of the coronary average peak flow velocity ($R =0.91, R^2$ 0.84, $p< 0.002$).

Conclusion: Coronary flow velocity decreased markedly in premature born lambs given a bolus doses of Indomethacin.

INTRODUCTION

Persistent ductus arteriosus (PDA) increases the risk of complications and worsens the prognosis of premature infants (1). Therefore early closure of PDA is usually reccomended. Indomethacin (IND), an inhibitor of prostaglandin synthesis, is widely used for closing symptomatic PDA in premature infants (2). IND has cardiovascular effects such as causing cardiac diastolic dysfunction in the premature infants (3). The negative effects of IND on cardiac function might be clinically significant in association with increased cardiac demand as evidenced for example by ST segment depression in the ECG of premature infants with PDA and respiratory distress syndrome (4). Its hemodynamic side effects such as reduction of blood flow to the brain, intestinal organs and kidneys, are well known (5-8). However, the effect of IND on coronary flow with clinically used doses is poorly documented. The aim of the study was to investigate the effects of clinical doses of 0.2 mg/kg of IND on coronary blood flow by using an Intracoronary Doppler Guide Wire (IDGW) in a premature newborn lamb model.

MATERIAL AND METHOD

Nine premature newborn lambs of mixed breed and gender were studied during the first day of life. Their gestational age varied between 132 and 134 days (term 145 days) and weight 3- 4.7 kg (median 3.9 kg). The investigation conformed with the Guide for the Care and Use of Laboratory Animals and accepted by the Ethical committee, University of Lund, Sweden.

Animals.

Pregnant ewes were premedicated with xylazine 6-8 mg i.m. before transportation to the laboratory. After sedation with ketamine 35 mg i.v. thiopental 650-800 mg was injected i.v. The trachea was intubated and anaesthesia maintained with isoflurane in nitrousoxid/oxygen. The lungs were ventilated with a Servo ventilator keeping the end-tidal pCO_2 at 4.5-6 kPa. Fluid balanced was maintained by infusing a balanced glucose/salt solution. Arterial pressure was monitored via an arterial cannula. Systolic blood pressure was maintained between 90 and 110 mmHg by adjusting the isoflurane concentration and infusing Ringer´s acetate as necessary. The abdominal wall and uterus of the ewes were opened and the head and neck of the lamb exteriorised. A 3, 5 or 4 mm inner diameter tracheal tube was inserted through an incision in the trachea. Air leaks were prevented by securing the tube. Catheters were inserted in the right jugular vein and right carotid artery. The lamb was then exteriorised and ketamine 8 mg and pancuronium 0.4 mg was given i.v. immediately after the umbilical cord was cut. The lamb was weighed, dried with towels, placed in an open incubator and covered with thin plastic sheets to reduce evaporative heat loss. Oesophageal temperature was kept at 38-39 ^{o}C with radiant heat lamps as needed. The tracheal tube was connected to a Servo Ventilator (model 900C; Siemens-Elema, Solna, Sweden) in pressure control mode. Initial ventilator settings were: inspiratory pressure 29 cm H_2O with 4 cm H_2O PEEP and ventilatory rate 50/min. Inspiratory time was 50% of the cycle and the fraction of inspired O_2 (Fi O_2) 0.5. The ventilator settings were subsequently adjusted to maintain PaO_2 at 6-8 kPa, and $PaCO_2$ at 5-6 kPa. A catheter was placed in the umbilical artery. Tip position in the lower abdominal aorta was confirmed with fluoroscopy. Systemic arterial blood pressure as well as pulmonary artery

pressure was monitored continuously. Blood from the ewe 10 ml/kg was given if the mean arterial pressure was less than 40 mmHg but if Hb exceeded 150 g/l, Ringer´s acetate was used instead. Blood was likewise given if Hb was less then 130 g/l. One mmol/kg sodium bicarbonate was given if the pH was less the 7.25 and base deficit more than 5 mmol/l. Sedation and analgesia after delivery was maintained with ketamine 1 mg/ml in 5 % glucose with infusion rate 4 ml/kg/h and fentalyl 10 μg/kg/h after an initial bolus dose of 20 μg /kg. To maintain paralysis pancuronium was administrated i.v. as needed. The lamb was allowed to stabilize for at least 2 hours after birth. A left lateral thoracotomy was performed in the fourth intercostal space. The lung was retracted, the pericardium opened and the arterial duct ligated.

A pre-calibrated ultrasonic blood flow transducer connected to a Transonic T101 flow meter was applied around the ascending aorta to measure cardiac output. Subcutaneous electrodes were sutured to the chest wall for a continuous ECG monitoring, and a pulse-oxymeter probe placed on the tail for continuous monitoring of O_2 saturation (Sp O_2). Hemodynamic stabilization was allowed for another 30 to 60 minutes before intracoronary flow velocities were measured.

Measurement of the coronary flow velocity.

A 4F right coronary angiography catheter (Judkins) was advanced through the introducer in the right carotid artery to the aortic root. A selective left coronary angiography was performed by contrast injection of Omnipaque 240. To measure coronary flow velocities, an Intracoronary Doppler Guide Wire (IDGW), 0.014 inch (0.36 mm), (Flowire, Cardiometrics, Inc, Mountain View, California, USA) was advanced through the coronary catheter into the proximal left anterior descending coronary artery (LAD) and its position was confirmed

by fluoroscopy. The position was kept constant by securing the probe tightly within the coronary catheter and conforming the position repeatedly by fluoroscopy. A Doppler signal was acquired with a 15-MHz piezoelectric ultrasound transducer at the end of the guide-wire. The transducer permitted velocity acquisition with a pulse repetition frequency up to 90 kHz from a sampling depth of 5 mm. The forward-directed ultrasound beam with 25-grade divergent angle sampled the coronary flow profile. A high quality signal was obtained by torque adjustment with reference to the amplitude display. Continuous flow profiles with simultaneous ECG were registered from LAD and recorded on videocassette. Doppler flow velocity spectra were analysed on-line for average peak velocity (APV), where APV was the time average value of the instantaneous peak velocities over two cardiac cycles. Diastolic peak flow velocity and systolic peak flow velocities were measured off-line, and averaged over three cardiac cycles.

A single bolus dose of IND 0,2 mg/kg (0,4 ml/kg) was given over 1 minute i.v. (2). The flow velocity was registered continuously until the flow returned to its preinjection level. Recovery time was defined as time between lowest APV after indomethacin injection until the APV had returned to the preinjection level. Arterial pressure was measured with pressure transducers, using the midchest level as the zero reference. Heart rate was obtained via a continuous ECG monitoring. Blood gas tensions, pH and Hb were measured with a Radiometer OSM 3 blood gas analyzer (Radiometer Copenhagen). SpO_2 was additionally monitored continuously by a pulse-oxymeter. After completing the experimental protocol the lambs were killed with an overdose of thiopenthal

Statistical analysis

Paired sample t-test was used to test the effect of indomethacin on blood pressure and heart rate. A simple regression analysis was used to find a correlation coefficient (r) between coronary flow velocity before and after IND, and the correlation between maximum lowering of flow velocity and recovery time. P-value < 0.05 was considered significant.

RESULTS

IND administration led to decrease in heart rate and cardiac output while blood pressure and rate pressure product (RPP) increased significantly (Table 1). APV decreased in all lambs after IND was injected ($p < 0.05$, Fig. 1). Maximal decrease of APV was 5 to 52 per cent (median 26) and appeared one to seven minutes (median 3) after administration of IND (Table 2). There was no correlation between the basal APV and its maximal reduction after IND. There was a large variation in the response of APV to IND. In a group of six lambs the decrease of APV was median 23 per cent (range 5 - 26). In the remaining three lambs the median of decrease was 50 per cent (range 47 - 52). The recovery time had an almost linear correlation to the maximal degree of decrease of APV ($R = 0.91$, $R^2 = 0.84$, $p < 0.002$, Fig.2).

DISCUSSION

PDA was closed surgically before IND was given in order to rule out the effect of varying ductal size on the coronary flow. IND in clinically used dosage of 0.2 mg/kg given as a bolus dose over one minute, decreased the APV by up to 50 per cent and its return to normal could take nearly an hour. As IND is generally the

international drug of choice for medical closure of PDA its side effects are important to know. In the treatment decision one has to consider the balance between potential complications and benefits.

Numerous studies show that IND has the disadvantage of not only constricting ductus arteriosus, but also decreasing the flow to several organs. The decrease of flow velocity mainly indicates vasoconstriction of the small resistance vessels but an effect on the larger conducting arteries cannot be ruled out. We cannot not calculate the actual flow and therefore not the resistance because the whole vascular bed is constricted as reflected as decreased flow velocity. The obtained percentage of flow changes calculated with the assumption that the diametes is unchanged leads to misleading numbers. IND inhibits prostaglandin synthesis by decreasing the activity of cyclooxygenase, which results in decreased secretion of vasodilating prostaglandins such as prostacyclin by the endothelial cells. Vasoconstricting leukotriene concentrations increase after aspirin which is a nonsteroidal anti-inflammatory drug (NSAID) similar to IND (9). IND given with arachidonic acid leads to contraction of cheek pouch arterioles of hamsters but not if given alone. This suggests that blocking of cyclooxygenase pathway leads to an increased production of vasocontracting leukotrienes (10,11). Release of leukotrienes could play a role in the constriction of the vessels due to treatment with NSAID.

The IDGW give reliable measurements of coronary flow velocity without interfering with it. It has been shown to cause negligible flow disturbance in coronary arteries as small as 1.2 mm in diameter (12).The method has been extensively validated both in vitro and in vivo (13,14). A close linear correlation exists between coronary flow velocity measured by the IDGW and volume of

flow measured by electromagnetic flow probes (13). The coronary flow velocity decreased in all lambs almost immediately (median 3 minutes) after the administration of IND. In some of the animals the decrease was substantial with the flow velocity reduction by 50 per cent and the effect remained up to an hour. The lambs that had the largest decrease in APV had also the longest recovery time . It is unclear what factors initiate such a big variation in the response of the coronary arteries to IND. The lambs with the greatest percentage of flow velocity reduction did not start out with the highest amount of coronary flow velocity. There was no significant difference between Hb, CO, HR, temperature or postnatal age of the lambs at the time when IND was given. No correlation was seen between CO, MAP and RPP and recovery time of the APV for the whole group of nine lambs. A variation in the production of leukotrienes might play a role.

Several studies report a decrease of blood flow in various vascular beds after IND administration. Cerebral blood flow has shown to decrease by up to 40 per cent two minutes post injection and remained at 35 per cent below pre-dose level for at least one hour. Blood pressure increased simultaneously by 15 per cent, one minute after injection of IND (15). Median recovery time of the flow in the superior mesenteric artery after IND was 50 minutes (16). Coronary flow was affected by intravenous IND administration in nine adults with coronary disease, with a simultaneous increase in arterial blood pressure and myocardial oxygen demand (17). The decreased diastolic function in premature infants post IND administration has been speculated to be due to coronary vasoconstriction and myocardial ischemia (3), which looks probable in the light of our results. A study by Klautz et.al. reports no reduction of coronary flow or left venticle

systolic function 30 and 60 minutes after a single dose of 1 mg/kg of IND. (18). However, this is not unexpected as the physiological changes have probably taken place already prior to these time points. In our study the maximal reduction of flow velocity always occurred in less then eight minutes. Myocardial oxygen consumption increased in all lambs after IND administration, demonstrated by an increase of RPP, which is the product of heart rate and mean blood pressure (19). Reduction of coronary flow leads to a decreased perfusion of the heart muscle and this in combination with simultaneous elevation of blood pressure, worsens the energy supply/demand ratio. This may cause a significant extra hemodynamic stress in already sick babies. Surveillance of the babies should be intensified during an immediate period after initiation of IND delivery. A stress-free period up to one hour after the IND administration avoiding suction of the trachea, feeding etc. seems reasonable.

Some centres, such as Lund, have changed the treatment regime to ibuprofen. However, one study on dogs showed reduced flow in coronary collaterals after ibuprofen injection (20). Other studies suggest that ibuprofen has less influence on flow and perfusion of organs as compared to IND. Ibuprofen seems to have no negative effect on cerebral, mesenteric and renal blood flow (21,22,23), but the effect on the PDA seems to be comparable (24,25). More information about ibuprofens effect on coronary flow is needed.

The limitations of our study are that we don’t have any documentation of myocardial perfusion and performance during administration of IND. Moreover, we did not have techniques to measure diameter of the coronary arteries during IND delivery.

In conclusion, IND can reduce the coronary flow velocity in lambs to less than half in less than 10 minutes. The APV may remain reduced up to almost one hour. IND can increase myocardial oxygen demand while simultaneously reducing myocardial flow and cardiac output, which can be detrimental for sick babies.

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FIGURES:

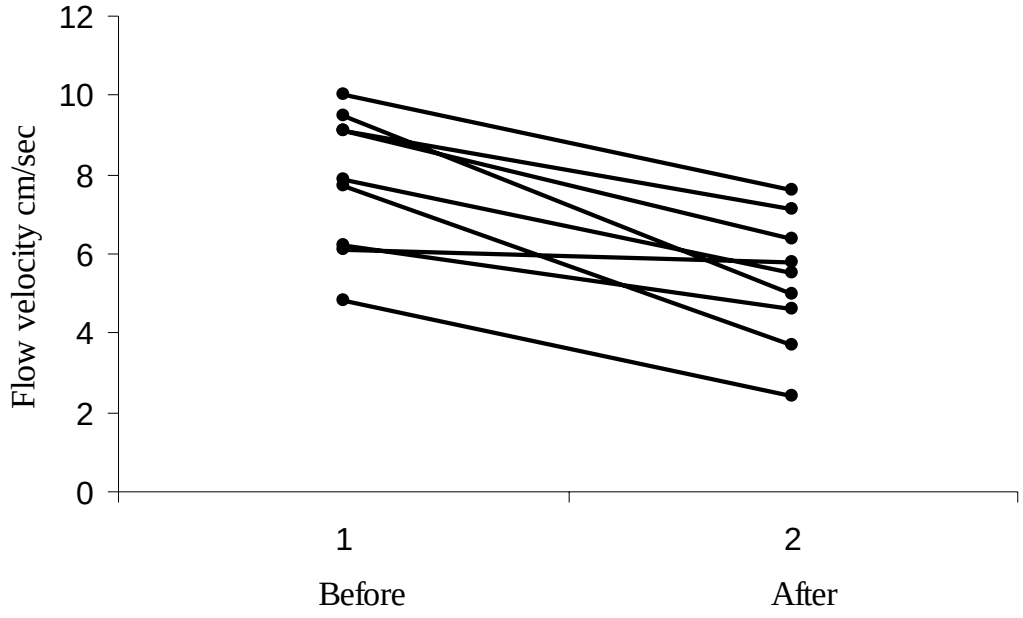

Figure 1. Coronary flow before and after indomethacin injection.

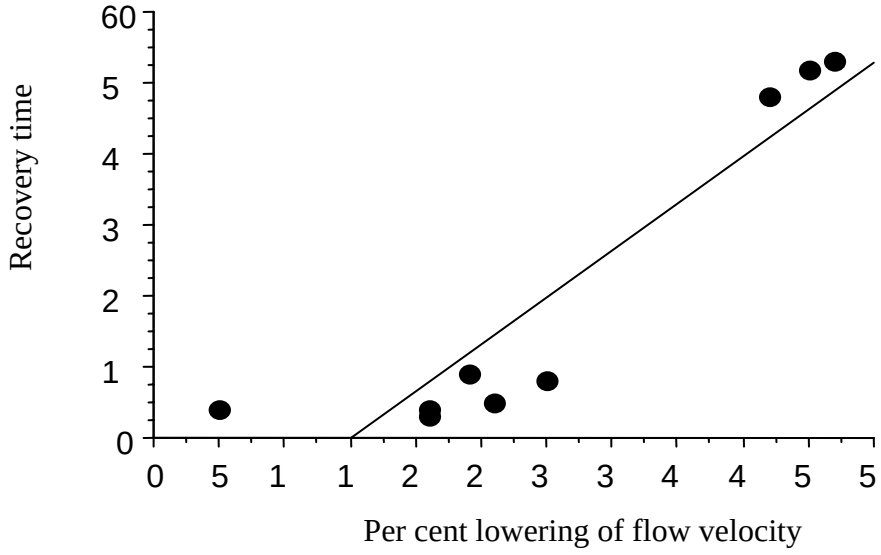

Figure 2. Maximal lowering of an average peak flow velocity in the left coronary artery as a function of recovery time.