Plasma free and sulfoconjugated catecholamines during acute asphyxia in the sheep fetus — relation to cardiovascular parameters*

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1 Introduction

Acute asphyxia of the fetus may be encountered during labor due to a variety of causes including compression of the umbilical cord, abruptio placentae, maternal shock, and prolonged contractions of the uterus. The fetal cardiovascular system reacts with a deceleration of the heart rate and an increase in blood pressure, reflecting a simultaneous activation of both the sympathetic and parasympathetic system [24]. Fetal acidosis and low Apgar values are associated with increased concentrations of free norepinephrine (NE), epinephrine (E) and dopamine (DA) in umbilical cord blood [17, 23, 25], while prolonged as well as repetitive episodes of asphyxia result in a rise of plasma free catecholamines in sheep fetuses [10, 11, 13, 20]. Circulating catecholamines have not been measured during and after one short period of complete reduction of uterine blood flow. It is well established that after its release from sympathetic nerve endings and the adrenal medulla free catecholamines are inactivated by several mechanisms including transformation into sulfoconjugated derivates, which are biologically inactive. No data are available on the concentrations of sulfoconjugated catecholamines during acute fetal asphyxia. Preliminary results in human fetuses indicate, that free as well as sulfoconjugated catecholamines are concomitantly increased during asphyxia [30]. Thus, the aim of the present study was to eludicate the role of sulfoconjugation for inactivation of free catecholamines after acute reduction of uterine blood flow for 5 minutes.

Furthermore, the correlation between free catecholamines and fetal cardiovascular parameters was studied.

2 Methods

The experiments were performed on five near term pregnant sheep (duration of pregnancy: $110-130$ days; fetal weight: 3250 g, range $1530-3900$). Prior to surgery, the sheep were kept in a separate room for 24 hours without food but with free access to water.

Preparation: After spinal anesthesia ($25-35$ mg tetracaine) and with intermittent intravenous injections of diazepam ($10-20$ mg) and ketamine ($200-500$ mg) the uterine horn was delivered by a midline abdominal incision and opened in an avascular area. A catheter was advanced via the femoral artery into the fetal aorta for blood sampling and measurement of arterial blood pressure as well as fetal heart rate. A second catheter was placed into the amniotic cavity for recording intrauterine pressure. An inflatable occluder was placed around the maternal aorta approximately 10 cm above the bifurcatio aortae to enable reversible complete reduction of uterine blood flow for a definite period of time. The complete reduction of uterine blood flow was verified by measurement of arterial maternal blood pressure below the aortal occlusion.

Experimental procedure: Experiments were performed $4-5$ days after operation. Fetal and maternal blood pressure as well as intrauterine pressure were measured via Statham transducers and

* Dedicated to Professor Dr. K.-H. WULF on the occasion of his 60th birthday.

monitored continuously. The recorded pulse pressure was used as trigger signal to obtain a beat to beat registration of fetal heart rate. By inflating the occluder around the maternal aorta complete reduction of uterine blood flow was achieved for a period of 5 minutes. Fetal arterial blood samples were taken before, 3 and 5 minutes after the start, and 2, 5, 10, and 30 minutes after release of the occlusion. In order to minimize pain for the ewe, spinal anesthesia was used 1 hour before occlusion of the maternal aorta.

Blood measurements: The following parameters were analyzed immediately: pH, Po_2, and Pco_2 (Technicon Blood Gas Analyzer), hemoglobin concentration and oxygen saturation (SO_2) (photometrical test, OSM 2 Hemoximeter, Radiometer), and lactate concentration in hemolyzed blood (Lactate Analyzer 640, Roche). Blood for catecholamine determination was collected in lithium-heparin tubes (Sarstedt No. 36377) and placed on ice without delay. After centrifugation for 10 minutes (4000 rpm) at $+2$ to $+4\,°C$, the plasma was kept frozen at $-25\,°C$ until assayed. The concentrations of free NE, E, and DA were measured radioenzymatically according to the principles of PEULER and JOHNSON [26]. We introduced several modifications to shorten the assay and to achieve higher reproducibility which were presented in detail previously [35]. The concentrations of sulfoconjugated NE, E, and DA were assayed by use of type VI arylsulfatase (Sigma, 64 mU/tube) coupled with the catechol-O-methyl-transferase reaction according to the method of JOHNSON et al. [12].

Statistical analysis: When appropriate, results are expressed as mean $\pm$ SEM, else median values and ranges are given. The U-test (Mann-Whitney) and Students t-test for paired data were used to test statistically significant differences. Assuming that the clearance obeys first order kinetics, the half life time of catecholamines after the end of asphyxia was calculated according to the following equation:

$$t\,1/2\,\text{min} = \frac{\ln 2 \times 10}{\ln\left(\dfrac{C\,0 - C\,\text{baseline}}{C\,10 - C\,\text{baseline}}\right)}$$

In this equation C baseline represents catecholamine concentrations during the control period, C 0 at the end of asphyxia and C 10 ten minutes after release of aortal occlusion.

3 Results

Due to total reduction of uterine blood flow asphyxia as well as metabolic acidosis developed. After the start of occlusion Po_2 and SO_2 declined rapidly and reached the zero line within 3 minutes (figure 1). Pco_2 increased from 44 ± 1 mm Hg during the control period to 98 ± 8 mm Hg at the end of occlusion, pH decreased from 7.33 $\pm$ 0.02 to 6.94 $\pm$ 0.02, lactate rose from 2.3 $\pm$ 0.2 to 7.1 $\pm$ 0.3 mmol/l, and hemoglobin concentrations increased from 8.3 $\pm$ 0.7 to 11.1 $\pm$ 0.9 g% (figure 2). After release of the occlusion, blood gases returned to baseline values within 3 to 5 minutes.

The fetal cardiovascular response to asphyxia consisted of a deceleration of heart rate and an increase in systolic and diastolic blood pressure as well as pulse pressure (figure 3). However, 3 minutes after starting the aortal occlusion, blood pressure declined but was still higher as compared to
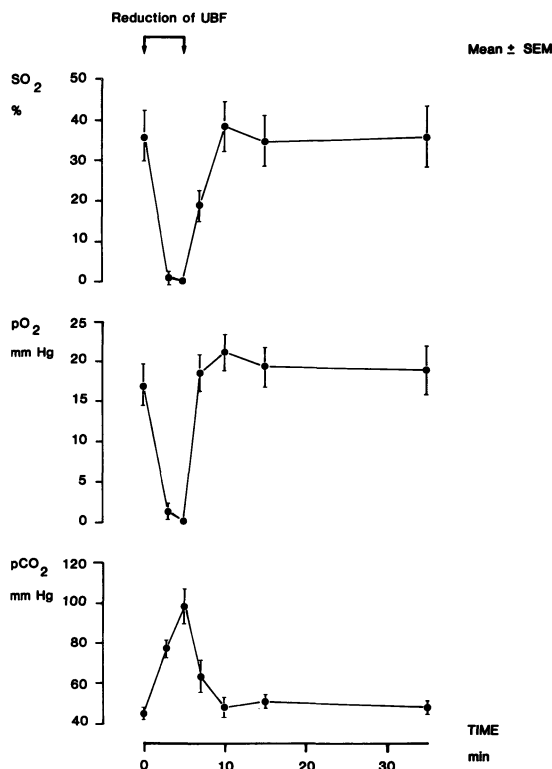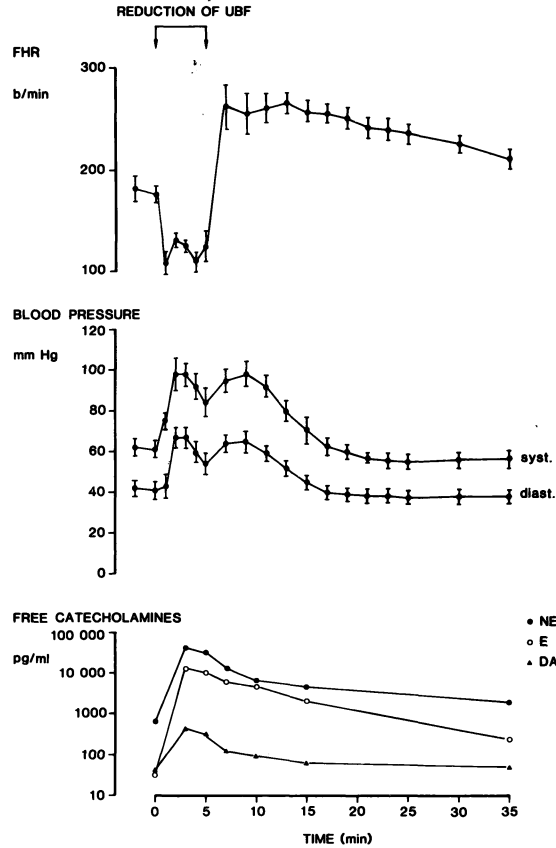

Figure 1. SO_2, Po_2 and Pco_2 in fetal arterial blood before, during, and after a 5 minute period of complete reduction of uterine blood flow (mean $\pm$ SEM; n = 5).
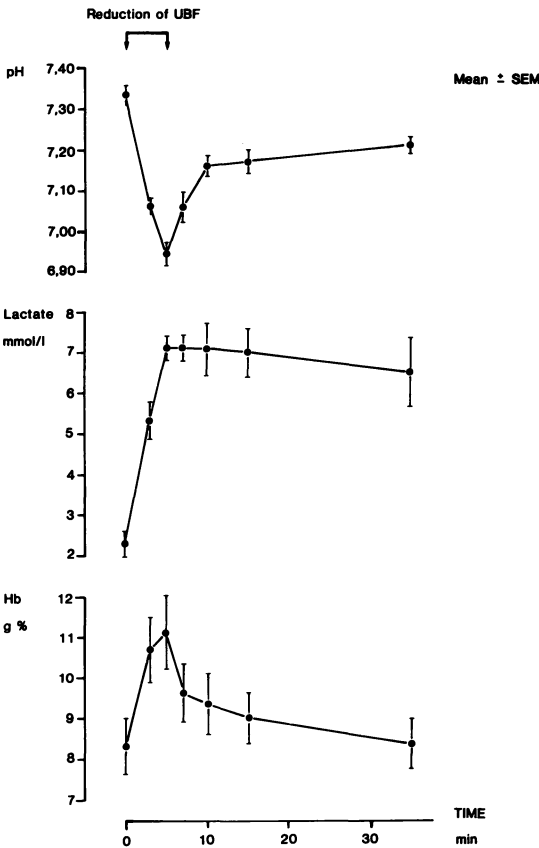
Figure 2. PH, lactate, and hemoglobin concentrations in fetal arterial blood before, during, and after a 5 minute period of complete reduction of uterine blood flow (mean ± SEM; n = 5).

Figure 3. Baseline fetal heart rate, systolic as well as diastolic blood pressure, and concentrations of free NE, E, and DA before, during, and after a 5 minute period of complete reduction of uterine blood flow (n = 5). Fetal heart rate and blood pressure are given as mean ± SEM, while concentrations of free catecholamines are depicted as median values.

control values (p < 0.01). After cessation of total reduction of uterine blood flow fetal tachycardia prevailed and blood pressure showed an initial increase before returning to baseline values. At the end of the observation period arterial blood pressure had reached control values whereas fetal heart rate remained elevated (210 ± 8 versus 176 ± 8 bpm; p < 0.05).

Concentrations of free catecholamines before, during, and after reduction of uterine blood flow are given in table I and figure 3. Peak concentrations were reached after 3 minutes of asphyxia. Median values of free NE were 60-fold higher as compared to the control period while the increase of free E was 370-fold and that of DA 13-fold. A wide range of concentrations for all amines could be observed. After release of aortal occlusion, free

catecholamines declined rapidly. Free NE and DA almost reached baseline values at the end of the observation period, while E was still 10-fold higher as compared to control values. As illustrated in table II, sulfoconjugated catecholamines showed a similar pattern to acute fetal asphyxia. Peak concentrations were reached within 3 minutes after starting the occlusion. Sulfoconjugated NE increased 40-fold, E 300-fold, and DA 10-fold as compared to baseline values. 30 minutes after the end of asphyxia, sulfoconjugated NE and DA were almost normalized, whereas sulfoconjugated E remained 5-fold increased. The half life time of free and sulfoconjugated catecholamines within the first 10 minutes after cessation of aortal occlu-

Table I. Concentrations of free catecholamines in fetal arterial plasma before, during, and after a 5 minute period of complete reduction of uterine blood flow (median values (range); n = 5; pg/ml)

	NE	E	DA
Control	660	30	35
	(350 − 1700)	(10 − 105)	(20 − 70)
Asphyxia			
3 min	40600	12300	470
	(32200 − 57600)	(7500 − 19000)	(170 − 900)
5 min	30400	9800	310
	(18900 − 43100)	(5050 − 20400)	(230 − 420)
Postasphyxia			
2 min	11600	5500	120
	(6200 − 21600)	(2900 − 15150)	(35 − 190)
5 min	6450	4650	85
	(3950 − 11330)	(2150 − 7500)	(35 − 105)
10 min	4500	2030	60
	(2150 − 7400)	(580 − 6940)	(40 − 120)
30 min	1700	230	50
	(780 − 2100)	(50 − 360)	(20 − 60)

Table II. Concentrations of sulfoconjugated catecholamines in fetal arterial plasma before, during, and after a 5 minute period of complete reduction of uterine blood flow (median values (range); n = 5; pg/ml)

|	NE	E	DA
Control	1580	45	125
	(895 − 3150)	(20 − 110)	(100 − 190)
Asphyxia			
3 min	58830	12900	1300
	(55070 − 129000)	(9000 − 32120)	(450 − 1500)
5 min	45750	13800	600
	(28500 − 89100)	(5500 − 33550)	(490 − 950)
Postasphyxia			
10 min	4750	750	165
	(2650 − 9500)	(360 − 4800)	(130 − 250)
30 min	2960	210	135
	(900 − 4100)	(35 − 300)	(110 − 200)

sion ranged from 2.5 to 4.3 minutes (table III). Half life times were not significantly different between free and conjugated amines.

The relationship between free NE and systolic blood pressure is illustrated in figure 4 for each experiment. Three minutes after complete reduction of uterine blood flow free NE as well as systolic blood pressure were markedly increased. In the following two minutes of asphyxia, both parameters declined concomitantly. Free NE rapidly decreased during the initial 5 minutes after release of occlusion, whereas blood pressure rose again. In the remainder of the postasphyxial pe-

riod, both free NE and systolic blood pressure reached control values.

Table III. Half life time of free and sulfoconjugated catecholamines within the first 10 minutes after cessation of complete reduction of uterine blood flow (median values (range); n = 5; min)

	NE	E	DA
Free	3.2	4.3	2.9
	(2.8 − 4.0)	(2.5 − 12.2)	(2.5 − 6.3)
Sulfo-conjugated	2.5	2.6	2.8
	(1.7 − 2.9)	(1.9 − 6.4)	(1.8 − 4.4)
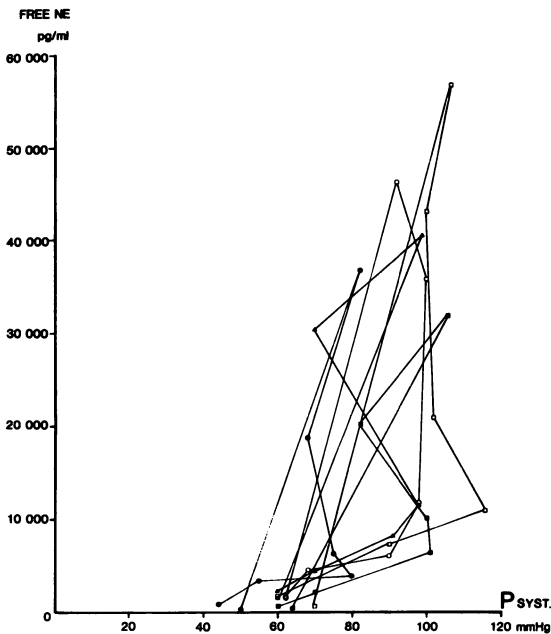
Figure 4. Systolic blood pressure versus free NE concentrations in fetal arterial blood before, 3 and 5 minutes after the begin, and 2, 5, 10, and 30 minutes after cessation of total reduction of uterine blood flow. Original data from the 5 experiments are given.

4 Discussion

In the present study, reversible acute fetal asphyxia was induced by occlusion of the maternal aorta. Reversibility was documented by the rapid normalization of fetal blood gases in the postasphyxial period. Aortal occlusion was used instead of compression of the umbilical cord to leave the feto-placental unit intact, since it is known, that the placenta is a major site of degradation of catecholamines [14, 25]. As a result of total cessation of blood flow to the hindquarters for 5 minutes, metabolic effects on the mother have to be taken into account. However, it seems unlikely that these affects should influence the fetus, since the syndesmochorial placenta of the sheep has a 10 to 20-fold lower permeability for electrolytes, lactate, and bicarbonate as compared to the hemochorial type of placenta [6, 18]. Furthermore, there is no evidence for materno-fetal transfer of catecholamines across the placenta [13]. Thus, it seems reasonable to infer that the experimental model used represents fetal asphyxia as under the conditions of a prolonged uterine contraction.

The fetal sympathoadrenal system is capable to release large amounts of free catecholamines into the circulation during alphyxia. While free NE is the predominant circulating amine, it is of note that the relative increase is highest for E. In comparison, DA reveals the weakest response to asphyxial stress [25]. Despite continued presence of the asphyxial stimulus, concentrations of free catecholamines declined after 3 minutes of complete reduction of uterine blood flow, indicating that secretion of free catecholamines decreases after a short period of maximal stimulation. Alternatively, the fall in free amines may also reflect increased catabolism at the same, i. e. unchanged rate of production. Plasma catecholamines are inactivated by several mechanisms including enzymatic degradation, neuronal reuptake, accumulation in red blood cells, and conjugation [1, 7, 27, 29]. These mechanisms seem to be effective in the sheep fetus near term, since concentrations of free catecholamines rapidly decline after termination of asphyxia. The half life time of free catecholamines approximates 3 to 4 minutes within the first 10 minutes of the postasphyxial period. In comparison, the half life time of infused free E ranged from 0.23 to 0.27 minutes in sheep fetuses [13]. The observed difference may be explained by the persistent secretion of high amounts of catecholamines into the circulation after cessation of reduction of uterine blood flow, which results in a prolongation of the half life time measured in our experiments.

It has been shown that enzyme inactivation of free catecholamines to sulfoconjugates is governed by phenolsulfotransferase (E. C. 2.8.2.1.), an enzyme which has been found in various organs [2, 4, 7, 8, 16, 28, 31]. Several investigations suggested, that phenolsulfotransferase activity is unable to match high rates of NE and E secretion following sympathoadrenal stimulation in adult man and experimental animals [5, 15, 32]. Our data in chronically instrumented sheep fetuses indicate, that the tremendous increase in plasma free catecholamines is regularly associated with a simultaneous increase in sulfoconjugates. Apparently, free catecholamines are readily sulfoconjugated upon entering the fetal circulation. These data are in accord with previous results obtained in human fetuses [30] where a concomitant rise in the amounts of free and sulfoconjugated catecholamines was found during asphyxial stress. After the release of complete reduction of uterine blood flow sulfoconjugated catecholamines were rapidly

removed from the fetal circulation with a half life tim of 2.5 to 2.8 minutes at least during the initial 10 minutes. It is obvious that in the sheep fetus sulfoconjugated amines do not persist much longer in the circulation than free catecholamines, which is at variance to adult healthy persons where sulfoconjugates have a half life time which is 3 to 7-fold longer as compared to free amines [19]. We suggest that these differences may be due mainly to species specific factors which include binding as well as metabolism of catecholamines [1, 3, 22, 33, 34]. Another explanation may result from the metabolic function of the placenta.

With regard to the functional significance of secretion of high amounts of free catecholamines during asphyxia, redistribution of fetal organ blood flow takes place with a marked increase in blood flow to the brain and adrenals, while blood flow to the spleen, kidneys, liver, and skin decreases significantly [10, 11]. The peripheral vasoconstriction may result in an extravasation of plasma fluid from the intravascular space, which is suggested by the significant increase in fetal hemoglobin concentrations [9]. Due to peripheral vasoconstriction and a positive inotropic effect of free catecholamines, which is documented by the rise in pulse pressure, systolic as well as diastolic blood pressure increased during the initial 3 minutes of asphyxia. Besides declining concentrations of free amines, the decrease of blood pressure during the following 2 minutes of asphyxia may be mainly due to asphyxial depression of the myocard [21]. After the end of occlusion, free catecholamines rapidly declined whereas blood pressure as well as pulse pressure rose again. It is obvious that this rise is caused by the effects of reoxygenation on myocardial performance. An improved myocardial contraction force along with tachycardia results in an increased ventricular output per minute while peripheral vasoconstriction remains effective during several minutes of the postasphyxial period [10, 11]. However, with declining catecholamine concentrations blood pressure returned to baseline values within 15 minutes after release of aortal occlusion. With regard to fetal heart rate, the deceleration observed after the onset of asphyxia is mainly due to vagal stimulation via chemoreceptors [24]. Following cessation of total reduction of uterine blood flow, the reoxygenation of fetal blood results in a decreasing activity of the parasympathetic system [24]. Consequently, the sympathetic system predominates, which is reflected by fetal tachycardia. There is a close correlation between fetal heart rate and free catecholamines, especially E, during the postasphyxial activity of the central sympathetic system — fetal tachycardia may be caused by a peripheral beta-1-receptor stimulation due to circulating free catecholamines.

For the clinician, our results indicate, that in unstressed, normoxic fetuses the cardiovascular system is capable to maintain basel fetal heart rate and blood pressure during a severe, acute asphyxia of 5 minutes duration. However, alterations of organ blood flow, especially to the brain and adrenals, have not been assessed in this study. Furthermore, beat-to-beat variability of fetal heart rate was not investigated. For maintenance of the basic functions of fetal circulation, a maximal sympathoadrenal stimulation with secretion of free catecholamines and a profound redistribution of fetal organ blood flow seems to be essential [11]. Following cessation of total reduction of uterine blood flow, complete reoxygenation of fetal blood is accomplished within 5 minutes and fetal arterial blood pressure has reached control values within 15 minutes. In contrast, fetal heart rate remains elevated for at least 30 minutes after the end of asphyxia, thus being a long time indicator of increased sympathetic nervous activity following acute fetal stress.

Summary

Changes of free and sulfoconjugated catecholamines were measured radioenzymatically during a 5 minute period of acute asphyxia in chronically instrumented sheep fetuses (n = 5). Due to total reduction of uterine blood flow asphyxia as well as metabolic acidosis developed (pH = 6.94 ± 0.02; Pco_2 = 98 ± 8 mmHG; lactate = 7.1 ± 0.3 mmol/l). Peak concentrations of free catecholamines were reached after 3 minutes; free NE increased 60-fold, free E 370-fold and free DA 13-fold as compared to control values. Concomitantly, sulfoconjugated catecholamines rose markedly and were 40-fold (NE), 300-fold (E) and 10-fold (DA) higher when compared to the control period. Thus, the results reveal that the fetal sulfoconjugating system is very effective and able to match high concentrations of free catecholamines entering the circulation. After release of occlusion, free and sulfoconjugated catecholamines decreased with a half life time of 2.5 to 4.3 minutes during the initial

10 minutes. A close correlation could be demonstrated between free catecholamines and fetal arterial blood pressure, however, with interference of the effects of desoxygenation on the myocard. Moreover, fetal tachycardia is related to circulating catecholamines, especially E, during the postasphyxial period.

Our results suggest, that in unstressed, normoxic fetuses the cardiovascular system is able to maintain basic functions (heart rate and blood pressure) during asphyxia for 5 minutes. In this context, a maximal sympathoadrenal stimulation with secretion of free catecholamines seems to be essential.

Keywords: Cardiovascular system, catecholamines, dopamine, epinephrine, fetal heart rate, fetal asphyxia, fetal shock, norepinephrine, sulfoconjugation.

Zusammenfassung

Freie und sulfokonjugierte Plasmakatecholamine bei akuter Asphyxie des Schaffeten — Beziehung zu kardiovaskulären Parametern

Ziel vorliegender Arbeit war es, beim Schaffeten in utero Veränderungen der freien und sulfokonjugierten Katecholamine während und nach einer fünfminütigen akuten Asphyxie im chronischen Experiment (n = 5) zu untersuchen. Als Folge der kompletten Unterbrechung des uterinen Blutflusses entwickelte sich eine Asphyxie sowie eine metabolische Azidose (pH = 6,94 ± 0,02; Pco_2 = 98 ± 8 mm HG; Laktat = 7,1 ± 0,3 mmol/l). Die höchsten Konzentrationen an freien Katecholaminen im fetal arteriellen Plasma wurden 3 Minuten nach Okklusionsbeginn gemessen; im Vergleich zur Kontrollperiode stiegen Noradrenalin um das 60fache, Adrenalin um das 370fache und Dopamin um das 13fache an. Zeitgleich kam es zu einem ausgeprägten Anstieg der sulfokonjugierten Katecholamine um das 40fache (Noradrenalin), 300fache (Adrenalin) bzw. 10fache (Dopamin). Diese Befunde deuten darauf hin, daß die freien Katecholamine sehr rasch nach ihrem Eintritt in den fetalen Blutkreislauf in biologisch inaktive Sulfokonjugate umgewandelt werden. In den ersten 10 Minuten nach Okklusionsende betrug die Halbwertszeit der freien und sulfokonjugierten Katecholamine 2,5 bis 4,3 Minuten. Es fand sich eine enge Korrelation zwischen freien Katecholaminen und dem fetal-arteriellen Blutdruck, wobei jedoch der kardiodepressorische Effekt der Asphyxie berücksichtigt werden muß. Darüber hinaus besteht ein Zusammenhang zwischen den Katecholaminspiegeln, besonders von Adrenalin, und der fetalen Tachykardie nach Okklusionsende.
Unsere Ergebnisse lassen den Schluß zu, daß das Herzkreislaufsystem eines normoxischen, nicht vorgeschädigten Feten eine akute, fünfminütige Hypoxieperiode ohne schwerwiegende Folgen bezüglich Blutdruck und basaler Herzfrequenz tolerieren kann. Für die Aufrechterhaltung der fetalen Zirkulation scheint eine maximale Stimulation des sympathoadrenalen Systems mit Ausschüttung von freien Katecholaminen und einer Umverteilung der Organdurchblutung wesentlich zu sein.

Schlüsselwörter: Adrenalin, Dopamin, fetale Herzfrequenz, fetale Asphyxie, fetaler Schock, kardiovaskuläres System, Katecholamine, Noradrenalin, Sulfokonjugation.

Résumé

Catécholamines plasmatiques libres et sulfoconjuguées au cours de l'asphyxie aïgue ches le fœtus de brebis — relations avec les paramètres cardiovasculaires

On a mesuré les variations des catécholamines libres et sulfoconjuguées par méthode radio-enzymatique pendant une période de 5 minutes d'asphyxie aigue chez des fœtus de brebis appareillés en continu (n = 5). Une asphyxie ainsi qu'une acidose métabolique se sont installés, secondaires à la suppression du débit sanguin utérin (ph = 6,94 ± 0,02, Pco_2 = 98 ± 8 mm Hg; lactates 7,1 ± 0,3 mmol/l). Les pics des concentrations des catécholamines libres ont été atteints en 3 minutes; la NE libre augmente 60 fois, la E libre 370 fois et la DA libre 13 fois par rapport aux valeurs témoins. De façon concomitante, les catécholamines sulfoconjuguées s'élèvent nettement et sont 40 fois (NE), 300 fois (E) et 10 fois (DA) plus élevées que pendant les périodes témoins. Ainsi, les résultats montrent que le système de sulfoconjugaison fœtal est très efficace et capable de s'adapter à des concentrations élevées de catécholamines entrant dans la circulation. Après l'arrêt de l'occlusion, les catécholamines libres et sulfoconjuguées diminuent avec une demi-vie de 2,5 à 4,3 minutes au cours des dix premières minutes. Une corrélation étroite a pu être mise en évidence entre les catécholamines libres et la pression artérielle fœtale, avec, cependant interférence des effets de la privation d'oxygène sur le myocarde. En outre, la tachycardie fœtale est corrélée aux catécholamines circulantes, particulièrement à E, au cours de la période post asphyxique.
Nos résultats suggèrent que chez les fœtus en dehors du stress, avec une oxygénation normale, le système cardiovasculaire est capable de maintenir les fonctions de base (fréquence cardiaque et pression sanguine) au cours d'une asphyxie de 5 minutes. Dans le contexte, une stimulation sympathique maximale avec sécrétion de catécholamines libres semble essentielle.

Mots-clés: Asphyxie fœtale, catécholamines, choc fœtal, dopamine, épinéphine, norépinéphrine, rythme cardiaque fœtal, sulfoconjugaison, système cardiovasculaire.

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