Mem. Fac. Agr. Kagoshima Univ., **23**, 109-120, 1987

Effects of a Calcium Antagonist (Nicardipine) on Cardiovascular Function in Goats

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Received for Publication September 9, 1986

Introduction

Various hypotensive agents have been developed in recent years, but their use for the management of gestational hypertension is limited. Only those agents which are most efficacious and yet have the least potential to reduce uterine blood flow and placental perfusion should be used to avoid fetal distress, which leads to serious problems in perinatal medicine. Nicardipine, a calcium antagonist, has been reported to have beneficial effects on cerebrovascular disorders[7,8,9] and hypertension[1,6,12,13] but with reference to its usefulness for the management of hypertension in pregnancy, much remains to be evaluated in animal experiments. In this study, goats were used because they have most commonly been used as chronic preparation in perinatology in Japan. The optimal dose of nicardipine for the goat was established, first. Then, effects of nicardipine on cardiovascular function in normotensive goats were compared with those on hypertensive goats experimentally induced by administering angiotensin II. In pregnant goats, additionally, placental transfer of the drug and the effect on uterine blood flow were investigated. Based on these results, whether or not nicardipine could be used for the management of gestational hypertension was studied.

Materials and Methods

1. Determination of the optimal dose in goats

Nippon Saanen goats were used. The animal was fixed in a lateral recumbent position and polyethylene catheters (PE90 INTRAMEDIC, Clay Adams) were inserted into the femoral artery and vein with local anesthesia. The catheters running subcutaneously along the abdominal wall were made to stick out of the flank. Then, the goat was housed in a cage and secured with a stanchion. The arterial catheter was attached to a pressure transducer (4-327-C, BELL & HOWELL) for arterial pressure recordings. Heart rate was calculated by a instant counting amplifier (Model 1321, NEC San-ei) based on cyclic changes in arterial pressure. All recordings were made on a polygraph (POLYGRAPH 360 system, NEC San-ei).

Three dose levels such as 0.01, 0.02, and 0.03 mg/kg were selected based on the results

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reported by TAKENAKA et al.[11] for the serial measurement, which was carried out 3 times on 3 goats, 5 times on 5 goats, and 7 times on 4 goats, respectively. Upon stabilization after surgical procedure, a portion of nicardipine solution was administered intravenously slowly over 1 min. Blood pressure and heart rate were measured 5, 10, 20, 30 and 60 min after the initiation of injection.

2. Effects on cardiovascular function in goats

1) Effects on cardiovascular function in normotensive goats

Six Nippon Saanen goats were used. Anesthesia was induced with a 15 mg/kg intravenous dose of sodium thiopental and then an endotracheal tube was inserted. The goats were ventilated mechanically and respiratory rate was regulated. Anesthesia was maintained with GOF (Gas-Oxygen-Fluothane). In addition to catheterization of the femoral vein and artery mentioned above, under observation by fluoroscopy, a Swan- Ganz catheter (93A-131-7F, American Edwards Laboratories) was inserted into the jugular vein and advanced so that the tip was placed in the pulmonary artery for pulmonary arterial pressure (PAP) and pulmonary arterial wedge pressure (PAWP) recordings. A thermister connector of the Swan-Ganz catheter was connected to a cardiac output computer (Model 9520A, American Edwards Laboratories) for measurement of cardiac output by a thermodilution methed (Fig. 1). Based on measured values of these parameters, cardiac index (CI), stroke index (SI), systemic vascular resistance (SVR), and plumonary vascular resistance (PVR) were calculated by equations given in Table 1. Additionally, blood samples were withdrawn from the femoral artery for blood gas determination with a blood gas analyzer (M165/2, Corning).

Goats were prepared more than 24 hours before the experiment and fixed in a prone position. To the goats was intravenously injected 0.02 mg/kg of nicardipine over 1 min. Each parameter was measured 5, 10, 20, 30 and 60 min after the initiation of intravenous injection.

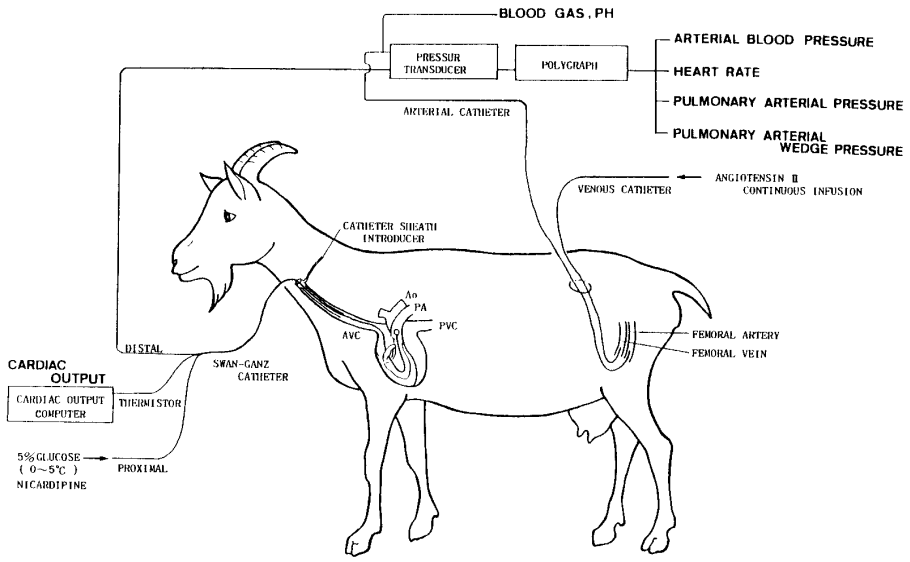

Fig. 1. Schema of the experimental model.

Table 1. Hemodynamic formulas

$SI = \frac{SV}{BSA}$	(mℓ/beat/m²)
$CI = \frac{CO}{BSA}$	(ℓ/min/m²)
$SV = \frac{CO}{HR} \times 1000$	(mℓ/beat)
$SVR = \frac{MAP - \overline{RAP}}{CI} \times 1332$	(dynes/sec/cm^{-5})
$PVR = \frac{\overline{PAP} - \overline{PAWP}}{CO} \times 80$	(dynes/sec/cm^{-5})

Legend :
CO = cardiac output
HR = heat rate
SV = stroke volume
SI = stroke index
BSA = body surface area
CI = cardiac index
MAP = mean arterial pressure
$\overline{RAP}$ = mean right atrial pressure
$\overline{PAP}$ = mean pulmonary arterial pressure
$\overline{PAWP}$ = mean pulmonary arterial wedge pressure
SVR = systemic vascular resistance
PVR = pulmonary vascular resistance

2) Effects on experimentally induced hypertensive goats

Six Nippon Saanen goats were used. The animals were prepared for experiment in a similar manner to that used in normotensive ones. Then, angiotensin II was injected into the femoral vein through the venous catheter. The initial dose was 0.005 μg/kg/min, which was progressively increased and adjusted to maintain diastolic femoral arterial pressure at a level which was 15-20 mmHg higher than normal, throughout the experimental period. Nicardipine was given at a dose of 0.02 mg/kg after the elevated diastolic pressure had been maintained for more than 30 min. Each parameter was measured in a similar manner to that used in normotensive animals. The initial elevated level was taken as a control.

3. Effects on uterine blood flow and fetal cardiovascular function in the pregnant goats

Four female Nippon Saanen goats which were estimated to be 110-140 days of gestation were used. Like a nonpregnant goat the pregnant animal was anesthetized and catheters were inserted into the artery and vein for the measurement of maternal blood pressure and heart rate. Then, the uterus was opened through a flank incision and catheters were inserted into the fetal jugular vein and carotid artery, and an endotracheal tube was placed. Electrodes for fetal ECG and intrauterine catheters were further installed and the fetus was replaced in the uterus. All the catheters and cord for ECG electrodes were brought outside from the flank so that the mother and fetal blood pressure and heart rate and intrauterine pressure can be monitored (Fig. 2). The blood flow of the uterine artery was monitored with an electromagnetic flow-meter (MFV-1200, Nihon Kohden). Recordings were continuously made on a polygraph (180-4, RECTI-HORIZ, NEC San-ei). Fetal blood gases were monitored.

Nicardipine was given to two normotensive and two hypertensive pregnant goats at an intravenous dose of 0.02 mg/kg a total of 6 and 5 times, respectively.

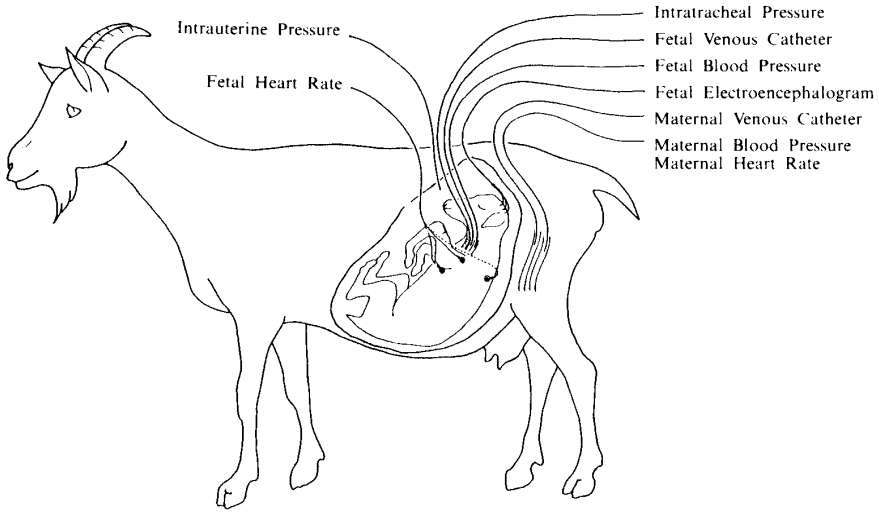

Fig. 2. Schema of the experimental model.

Results

1. Determination of the optimal dose for goats

As shown in Table 2, both blood pressure and heart rate changed, depending on the dose. There was essentially no fall in blood pressure after a 0.01 mg/kg dose of nicardipine, but the injection at doses of 0.02 and 0.03 mg/kg produced significant falls. The fall in diastolic pressure was greater than that in systolic pressure. Five min after injection, the pressure marked the lowest level; blood pressures in animals receiving 0.02 and 0.03 mg/kg nicardipine were 14 ± 2.1 and 16 ± 2.2 mmHg, respectively, lower than that in controls. The blood pressure recovered gradually. The falls in blood pressure after a dose of 0.03 mg/kg were greater and lasted somewhat longer than those after a dose of 0.02 mg/kg, although not significant.

All the three doses of nicardipine increased heart rate. Although the increase after a dose of 0.01 mg/kg was very slight, heart rates increased markedly to 48 ± 11.4 and 62 ± 10.4 beats/min 5 min after the injection at 0.02 and 0.03 mg/kg, respectively. Thus, the increase after 0.03 mg/kg was greater than that after 0.02 mg/kg and was significant even after 30 min (Fig. 3).

2. Effects on cardiovascular function in goats

The results are shown in Table 3 and Fig. 4 and 5. The rate of angiotensin II injection used to make the goats hypertensive averaged 0.023 μg/kg/min.

The peripheral arterial pressure was decreased maximally 5 min after injection of nicardipine in both normotensive and hypertensive animals. The decrease in diastolic pressure is greater than that in systolic pressure. The responses for hypertensive animals were greater than those for normotensive animals. The decreases in mean blood pressure were significant at 5 min and 10 min after injection (Fig. 6). For hypertensive goats, the pressure was significantly decreased even after 60 min ($p<0.05$).

The administration of nicardipine increased heart rate similarly in both hypertensive and normotensive groups.

Table 2. Hemodynamic effects of nicardipine in three experimental groups

Dose	Hemodynamic Variable	Time after administration (min) 5	10	20	30	60
0.01 mg/kg	SAP (Δ mmHg)	−3±1.2	−4±1.0	−3±1.9	−3±2.3	+1±2.7
	MAP (Δ mmHg)	−1±0.5	−2±1.6	0±0.8	+2±1.2	+1±1.2
	DAP (Δ mmHg)	−2±2.0	−2±2.1	+3±3.5	+2±3.2	+1±0.9
	HR (Δ beats/min)	+17±2.3	+4±2.7	+2±6.4	+2±1.9	+1±2.5
0.02 mg/kg	SAP (Δ mmHg)	−9±3.4	−7±3.5	−6±3.0	−5±2.5	−4±2.0
	MAP (Δ mmHg)	−12±2.3**	−8±1.9*	−6±2.0*	−3±1.7	−4±1.4
	DAP (Δ mmHg)	−14±2.1**	−9±2.0*	−6±2.5	−3±2.2	−3±1.8
	HR (Δ beats/min)	+48±11.4*	+37±10.0*	+30±11.4	+19±13.7	+6±4.5
0.03 mg/kg	SAP (Δ mmHg)	−8±2.1**	−5±2.7	−5±3.9	−7±3.8	−7±4.4
	MAP (Δ mmHg)	−13±1.7***	−8±2.7*	−9±3.3*	−8±3.8	−6±4.0
	DAP (Δ mmHg)	−15±2.2***	−9±2.8*	−9±3.1*	−8±3.9	−4±3.9
	HR (beats/min)	+62±10.4***	+52±9.0**	+30±7.5**	+20±8.0*	+5±5.1

*P<0.05, **P<0.01, ***P<0.001 compared with control (mean ± SE)

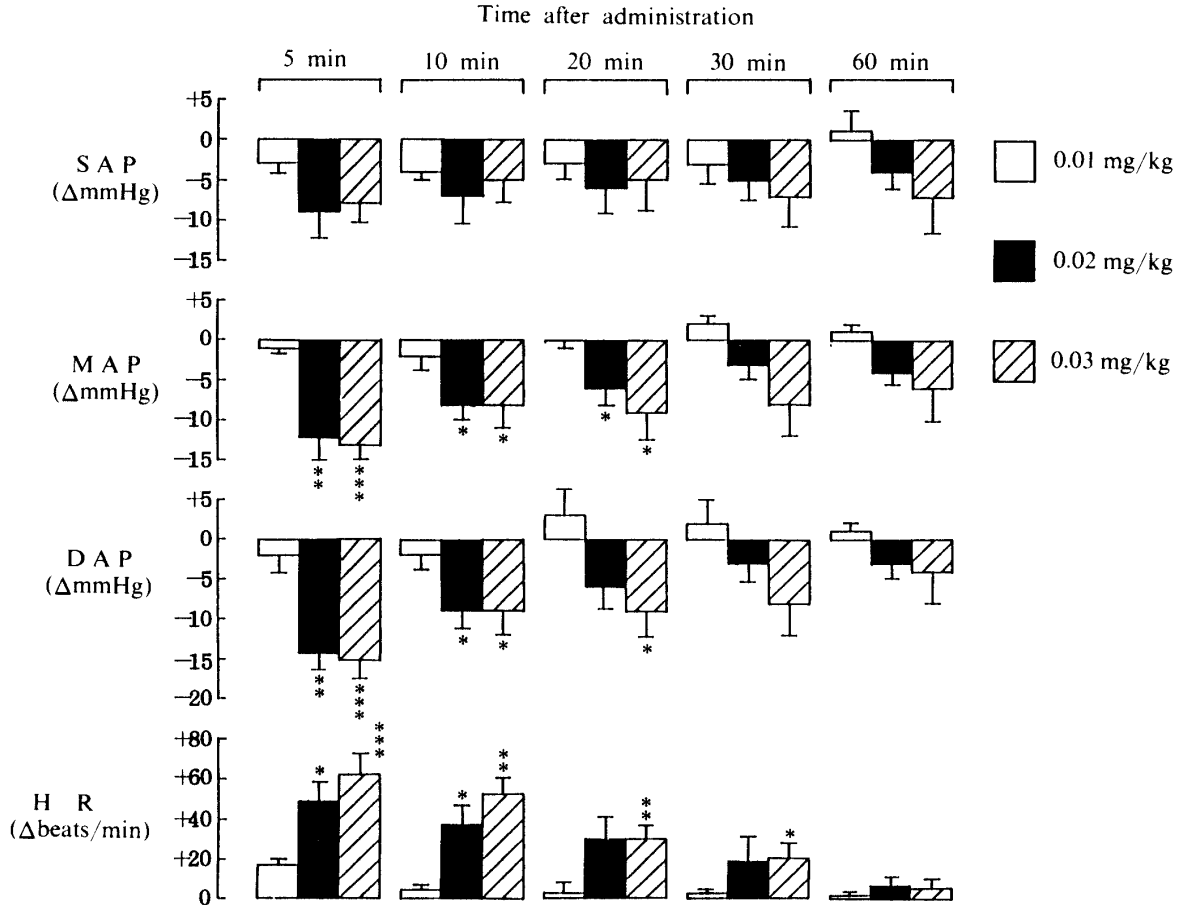

Fig. 3. Differences from control of systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), and heart rate (HR) in the three experimental groups.

*P<0.05, **P<0.01, ***P<0.001 compared with control

Table 3. Hemodynamic effects of nicardipine in normotensive and hypertensive goats

	Hemodynamic Variable		Control	Time after administration (min) 5	10	20	30	60
Normotensive Goats (n=6)	SAP	(mmHg)	123±4.1	116±3.2*	116±3.0	119±2.7	121±1.2	123±4.3
	MAP	(mmHg)	95±4.5	84±2.9*	84±2.4	88±2.2	90±2.0	93±3.1
	DAP	(mmHg)	75±3.7	59±2.2*	62±1.8*	66±3.0	72±2.2	75±2.0
	HR	(beats/min)	87±6.2	153±14.8**	153±17.8**	140±16.7**	117±14.0*	98±8.8*
	PAP	(mmHg)	12±1.1	15±1.2*	15±1.5*	15±2.1	15±2.4	15±2.1
	PAWP	(mmHg)	4±0.6	4±1.4	4±1.5	3±0.8	3±0.8	3±0.8
	CI	(ℓ/min/kg)	0.16±0.014	0.23±0.020**	0.22±0.016***	0.20±0.020*	0.19±0.019*	0.16±0.010
	SI	(mℓ/beat/kg)	1.81±0.122	1.56±0.158**	1.56±0.215	1.51±0.184*	1.69±0.189	1.71±0.148
	SVR	(%)	100±0	61±5.3***	64±5.7***	74±7.0**	80±5.0*	94±4.7
	PVR	(%)	100±0	92±8.0	97±10.8	112±12.0	118±18.9	129±18.1
	pH		7.43±0.028	7.43±0.033	7.43±0.023	7.44±0.033	7.45±0.034	7.44±0.036
	PO_2	(mmHg)	82±3.5	82±8.3	74±4.0	78±5.1	78±6.3	76±5.2
	PCO_2	(mmHg)	37±1.2	34±1.7	35±1.6	36±2.0	37±2.0	35±1.9
Hypertensive Goats (n=6)	SAP	(mmHg)	142±6.7	114±4.9***	118±5.3***	130±4.9*	131±3.7*	132±3.3*
	MAP	(mmHg)	112±6.0	83±6.1***	87±6.4***	99±6.1***	102±5.4**	103±4.7*
	DAP	(mmHg)	95±5.8	65±6.5***	70±7.0***	82±6.9***	84±6.3**	86±5.7*
	HR	(beats/min)	102±13.6	163±7.0**	155±7.0**	126±12.1	121±11.2**	118±16.9
	PAP	(mmHg)	18±3.4	18±2.8	18±3.4	20±4.3	18±2.9	17±3.3
	PAWP	(mmHg)	6±1.4	5±1.5	5±1.5	5±1.7	5±1.8	5±1.3
	CI	(ℓ/min/kg)	0.15±0.019	0.21±0.017**	0.20±0.014**	0.19±0.018***	0.18±0.015*	0.21±0.021
	SI	(mℓ/beat/kg)	1.63±0.308	1.33±0.128	1.34±0.149	1.53±0.187	1.57±0.215	1.78±0.413
	SVR	(%)	100±0	52±4.2***	57±4.3***	70±2.6***	75±4.4***	78±7.9*
	PVR	(%)	100±0	87±11.4	95±14.7	105±13.5	95±10.9	96±17.5
	pH		7.42±0.028	7.46±0.032	7.42±0.035	7.43±0.032	7.43±0.031	7.44±0.033
	PO_2	(mmHg)	78±3.1	80±5.1	72±3.9	76±6.9	72±3.9	77±4.1
	PCO_2	(mmHg)	35±1.2	32±1.9	33±1.6	33±1.6	33±1.4	34±2.3

*P<0.05, **P<0.01, ***P<0.001 compared with control (mean ± SE)

Nicardipine also markedly increased CI in both groups. However, the effects on SI and PAP in the two groups were somewhat different; the administration decreased SI and increased PAP in normotensive goats, but produced no significant change in these two parameters for hypertensive goats.

In normotensive and hypertensive goats receiving nicardipine, the SVR value was decreased after injection, reflecting the action as a peripheral vasodilator, but PAWP, PVR, and blood gases were not affected.

3. Effects of nicardipine on fetal uterine blood flow in pregnant goats

As shown in Table 4, changes in maternal blood pressure and heart rate in both hypertensive and normotensive pregnant goats are similar to those in the corresponding nonpregnant goats. Intrauterine pressure was not affected by nicardipine.

Uterine blood flow decreased to 89±1.4 and 89±3.3 % of control level in normotensive and hypertensive goats, respectively. The decreases are as small as about 11 %, but significant in both groups. The blood flow almost recovered after 20 min in both groups (Fig. 7).

The injection of nicardipine did not affect fetal blood pressure, heart rate, or blood gases.

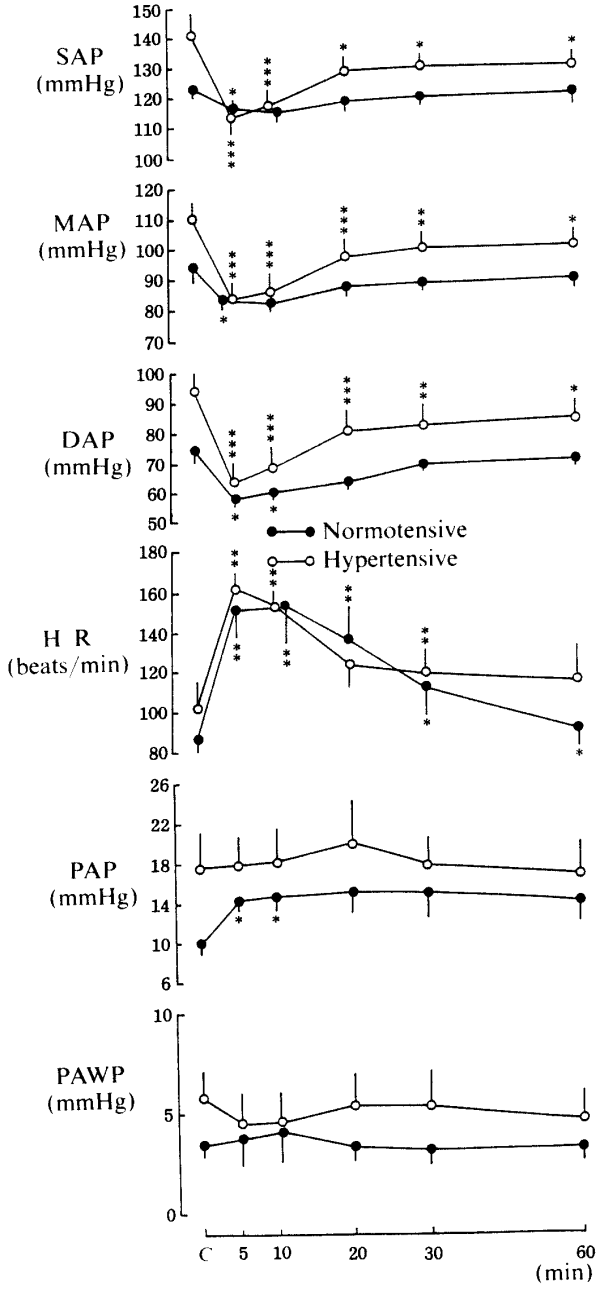

Fig. 4. Changes in systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), heart rate (HR), pulmonary arterial pressure (PAP), and pulmonary arterial wedge pressure (PAWP) before (C) and after intravenous injection of nicardipine.
*P<0.05, **P<0.01, ***P<0.01 compared with control

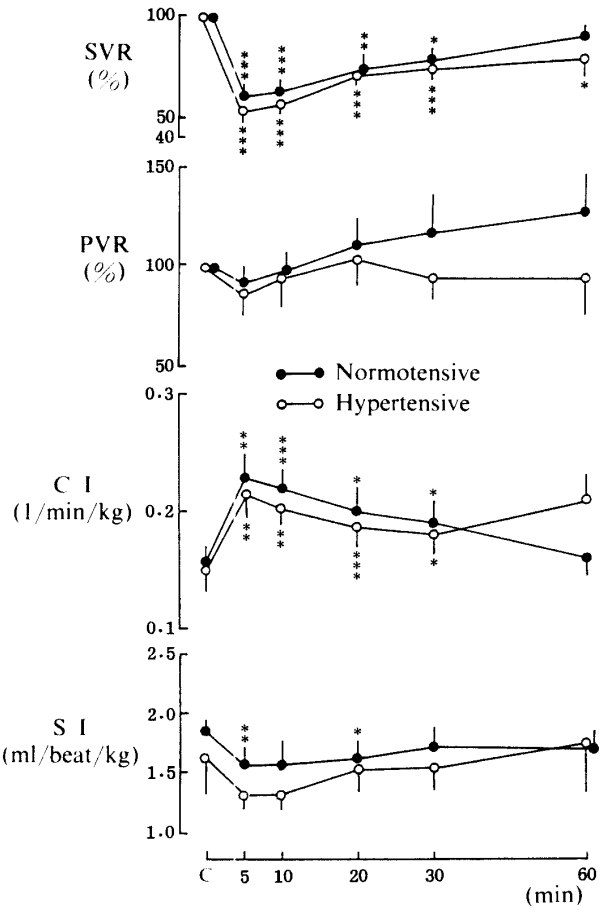

Fig. 5. Changes in systemic vescular resistance (SVR), pulmonary vascular resistance (PVR), cardiac index (CI), and stroke index (SI) before (C) and after intravenous injection of nicardipine.
*P<0.05, **P<0.01, ***P<0.001 compared with control

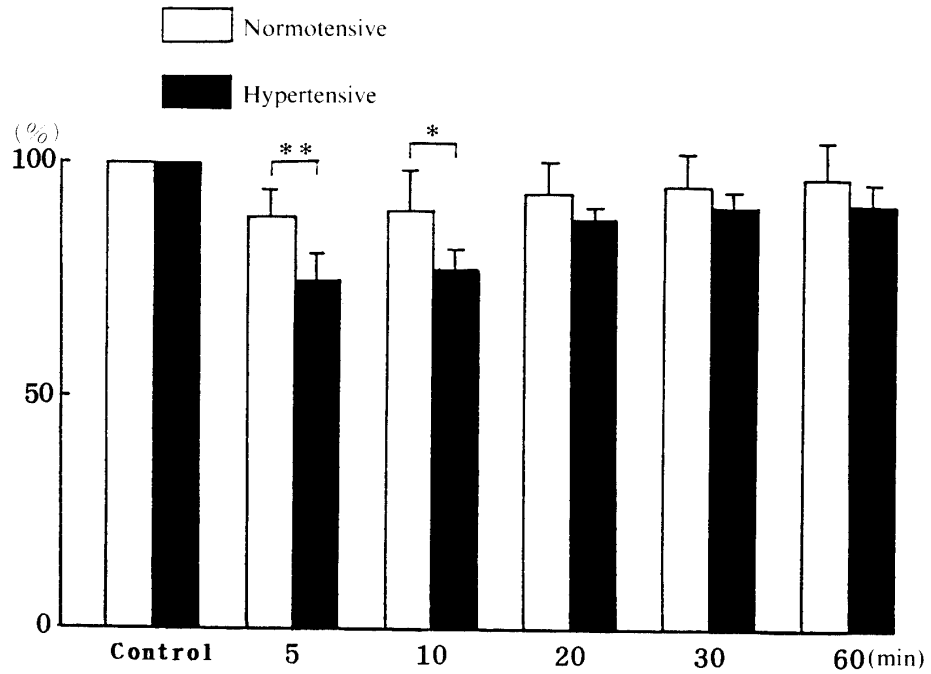

Fig. 6. Per cent changes in mean arterial pressure following the administration of nicardipine in the two experimental groups.
*P<0.05, **P<0.01

Table 4. Hemodynamic effects of nicardipine in normotensive and hypertensive pregnant goats

	Hemodynamic Variable		Control	Time after administration 5	10	20	30	60
Normotensive Pregnant Goats (n=6)	M-SAP	(mmHg)	115±6.2	115±3.4	115±4.8	117±5.9	120±4.5	117±5.7
	M-MAP	(mmHg)	77±2.5	69±2.5	72±1.4	73±2.2	77±1.9	73±1.1
	M-DAP	(mmHg)	57±3.2	46±3.4**	50±2.7**	51±2.8**	56±3.5	52±3.4
	M-HR	(beats/min)	102±4.5	148±4.1**	136±5.4**	120±6.3	116±5.1	109±2.4
	UBF	(%)	100±0	89±1.4***	94±2.4*	95±3.5	101±2.9	102±4.5
	F-SAP	(mmHg)	57±2.2	57±1.3	59±0.9	55±1.8	58±2.0	58±1.3
	F-MAP	(mmHg)	40±1.5	39±0.8	40±0.3	38±0.8	40±1.0	40±0.5
	F-DAP	(mmHg)	31±1.0	30±0.9	31±0.7	30±0.6	31±1.0	30±0.8
	F-HR	(beats/min)	189±7.6	193±4.5	193±6.1	188±3.8	183±6.5	183±4.6
	F-pH		7.31±0.025	7.34±0.025	7.32±0.026	7.34±0.026	7.31±0.032	7.32±0.031
	F-PO_2	(mmHg)	17±0.8	17±0.9	17±0.9	17±1.1	17±1.0	17±0.7
	F-PCO_2	(mmHg)	42±1.7	39±1.4	40±1.3	43±0.9	39±1.3	38±0.5
Hypertensive Pregnant Goats (n=5)	M-SAP	(mmHg)	139±8.7	133±8.0*	129±7.0	128±6.7	127±7.1	136±7.5
	M-MAP	(mmHg)	104±7.8	87±5.0*	90±5.4*	92±5.1*	93±5.8*	101±7.2
	M-DAP	(mmHg)	86±7.4	64±3.5**	70±4.7*	74±4.5*	75±5.4**	84±7.0
	M-HR	(beats/min)	91±11.0	174±7.1	158±10.9	135±10.9	118±11.7	103±13.1
	UBF	(%)	100±0	89±3.3*	92±3.0*	103±5.5	110±5.5	110±3.3*
	F-SAP	(mmHg)	53±2.6	53±2.3	51±1.8	50±2.2	50±2.3	52±1.9
	F-MAP	(mmHg)	36±1.4	34±1.4	32±1.2	33±1.5	33±1.9	33±1.4
	F-DAP	(mmHg)	26±1.5	24±1.2	23±1.0	25±1.3	25±1.7	24±1.3
	F-HR	(beats/min)	203±6.3	207±5.0	210±6.5	204±6.0	205±6.7	205±5.6
	F-pH		7.36±0.007	7.36±0.006	7.36±0.006	7.36±0.006	7.36±0.006	7.35±0.013
	F-PO_2	(mmHg)	18±3.4	16±2.5	16±3.4	17±2.7	19±2.4	17±2.5
	F-PCO_2	(mmHg)	34±3.3	35±0.8	35±1.7	37±2.1	36±0.7	38±1.8

*P<0.05, **P<0.01, ***P<0.001 compared with control M : maternal, F : fetal (mean ± SE)

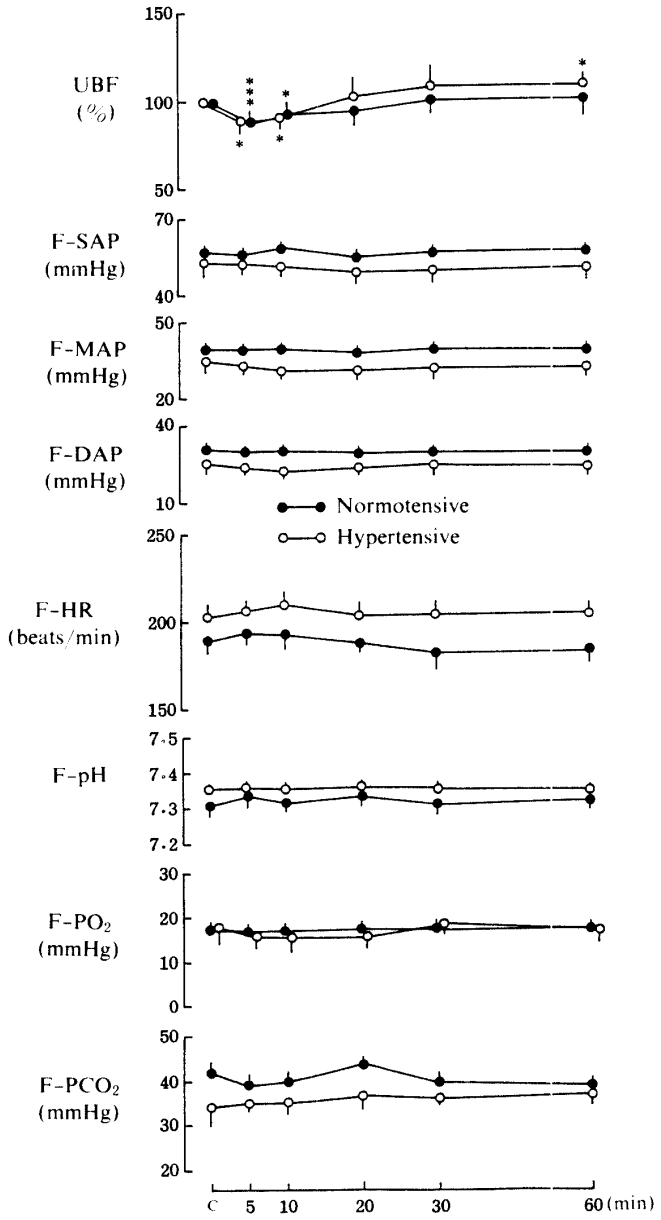

Fig. 7. Changes in utero-placental blood flow (UBF), fetal systolic arterial pressure (F-SAP), mean arterial pressure (F-MAP), diastolic arterial pressure (F-DAP), heart rate (F-HR), pH, and gases before (C) and after intravenous injection of nicardipine.
*$P<0.05$, ***$P<0.001$ compared with control

Discussion

Of three major symptoms of toxemia of pregnancy (edema, proteinuria and hypertension), hypertension is frequently subjected to medication. Medication to pregnant women, however, requires circumspection, because drugs may affect both the mother and fetus and pregnant women may differ from normals in metabolism.

This study aims at providing basic data for the treatment of gestational hypertension with nicardipine, a new antihypertensive agent. Using both normotensive and hypertensive goats, which have been the most common animals used as chronic preparation in perinatology, some effects of nicardipine on fetal and maternal cardiovascular function were investigated. Hypertensive goats were prepared by administering angiotensin II.

Intravenous administration of nicardipine produced adequate responses at 0.02 or 0.03 mg/kg in goats, but their responses were poor at 0.01 mg/kg. The decrease in diastolic pressure was greater than that in systolic pressure. However, an increase in heart rate after a dose of 0.03 mg/kg was larger than at 0.02 mg/kg.

According to TAKENAKA *et al.*[10], the increase in heart rate after administration of nicardipine was attributed to the increased reflex sympathetic activity secondary to a fall in blood pressure through baroreceptors, because an increase in heart rate after nicardipine was abolished by either bilateral vagotomy and carotid sinus neurectomy and pretreatment with β-blockers in dogs[11]. In conscious dogs, vasodilators have been reported to increase heart rate following stimulation of atrial stretch receptor or following cancellation of parasympathetic inhibition on sinus node, secondary to an increase in venous return[5]. In case of nicardipine, the fall in diastolic pressure was greater than that in systolic pressure. This indicates the drug exerts the action on resistant vessels[3], possibly leading to an increase in venous return. Thus, the increased venous return might contribute to a part of the increase in heart rate. The increase in heart rate, however, increases myocardial oxygen consumption, which is one of the annoying side effects. Therefore, 0.02 mg/kg dose was believed to be advantageous over 0.03 mg/kg dose and taken as the optimal dose to be used in this study in goats.

Nicardipine lowered blood pressure to a greater extent in hypertensive goats than in normotensive goats. This difference was mainly attributed to the persistent contraction of the vascular smooth muscles due to angiotensin II. It is likely that the persistent contraction makes the smooth muscle cells more dependent on extracellular Ca concentration.

A reduction in SI and an elevation of PAP occurred only in normotensive goats. The increased heart rate is mainly responsible for the decrease in SI. And, for hypertensive goats, contraction of the peripheral vessels due to angiotensin II administration increased after load, leading to a decrease in venous return and, although not significant, in SI. Therefore, it is likely that improvement of hemodynamics based on reduction of after load by nicardipine has masked such untoward effects in hypertensive animals.

The uteroplacental blood flow was reduced, by about 11 %, in both normotensive and hypertensive goats without change in blood pressure[7], heart rate, or blood gases in fetuses. Nicardipine may exert an adequate hypotensive action on mother with minimal adverse effect against fetuses.

Hydralazine is the primary hypotensive agent currently used to control hypertension in pregnancy. This diuretic has been reported not to change placental blood flow[2], but may aggravate myocardial ischemia by increasing myocardial oxygen consumption, because the agent, lacking ability to dilate coronary arteries, increases heart rate secondary to an elevation of reflex sympathetic activity, and thereby cardiac work.

Beta adrenergic blocking agents have also a disadvantage that their negative inotropic action reduces contractile forces of the cardiac muscles and heart rate.

Nicardipine is a Ca antagonist, which can dilate coronary arteries, and has been

reported to increase coronary blood flow[11]. In addition, in this study, nicardipine reduced blood pressure moderately without adverse effects on hemodynamics. The hypotensive effects appeared rapidly in hypertensive goats, but CI was satisfactorily maintained so as not to reduce blood flow in major organs, and the reduction in placental blood flow was slight without any evidence indicating harmful effects on fetuses. Nicardipine, which dilates the blood vessels by a direct effect on vascular smooth muscles[4,8,13] without suppressive effects on the autonomic nervous system, does not affect the normal circulatory reflex system. Therefore, nicardipine is one of the safest drugs from the viewpoint of maintenance of homeostasis. Thus, the present study fully presents the usefulness of nicardipine in the use for the management of gestational hypertension.

Summary

This study was undertaken to assess the hemodynamic effects of nicardipine in awake goats. Nicardipine, 0.02 mg/kg administered intravenously over 1 min, resulted in the following cardiovascular changes.

1) Nonpregnant goats

The peripheral arterial pressure was decreased maximally 5 min after injection of nicardipine in both normotensive and angiotensin-induced hypertensive goats. The decrease in diastolic pressure is more than that in systolic pressure. The response for hypertensive group was stronger than those for normotensive groups. The administration of nicardipine increased heart rate similarly in both groups. The administration decreased stroke index and pulmonary arterial pressure in normotensive goats, but produced no significant change in these two parameters for hypertensive goats.

2) Pregnant goats

Changes in maternal blood pressure and heart rate in both hypertensive and normotensive pregnant goats were similar to those in the corresponding nonpregnant goats. Uterine blood flow decreased to 89 ± 1.4 and 89 ± 3.3 % of control level in normotensive and hypertensive goats, respectively. The blood flow was almost recovered after 20 min in both groups. The injection of nicardipine did not affect fetal blood pressure, heart rate or blood gases.

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