Effects of a Low, Oral Dose of Nisoldipine on the Systemic and Coronary Hemodynamics and the Prostaglandin Metabolism of Ischemic Heart Disease Patients

Akira KURITA, M.D., Bompei TAKASE, M.D., Akimi UEHATA, M.D.,
Hiroko SUGAWARA, M.D., Toshihiko NISHIOKA, M.D.,
Toshiharu MARUYAMA, M.D., Kimio SATOMURA, M.D.,
Shuji KONDO, M.D., Kyoichi MIZUNO, M.D.,
Kazushige ISOJIMA, M.D., Haruo NAKAMURA, M.D.,
Toshikazu KANDA, Ph.D.,* and Yoshio YOSHINO, M.D.*

SUMMARY

This study investigated the effects of a low dose of nisoldipine (5 mg, p.o.) in 10 patients with ischemic heart disease. The patients were subjected to a 90-min exercise regimen before and after a 5 mg dose of nisoldipine, using a supine bicycle ergometer adjusted to each patient's limitations. The mean blood plasma level of nisoldipine was 3.8 ± 3.1 (SD) ng/ml. The drug significantly decreased the systolic arterial pressure in patients throughout the experimental session, whereas a change in the diastolic arterial pressure appeared only at the submaximal stage of the exercise. Additionally, at maximal exercise, nisoldipine caused a decrease in the mean coronary sinus pressure from 11.4 ± 7 mmHg to 6.5 ± 5 mmHg ($p < 0.01$). By contrast, while at rest, nisoldipine decreased the coronary vascular resistance from 1.5 ± 0.7 mmHg/ml/min to 1.0 ± 0.7 mmHg/ml/min ($p < 0.05$). After exercise, the drug decreased thromboxane B_2 levels from 1133 ± 907 pg/ml to 720 ± 379 pg/ml ($p < 0.05$) in the coronary sinus blood, and increased the 6 keto-prostaglandin $F_{1\alpha}$ levels from 465 ± 135 pg/ml to 559 ± 167 pg/ml ($p < 0.05$) in brachial artery blood. This suggests that a low, oral dose of nisoldipine can moderately improve the systemic and coronary hemodynamics and afterloads, and may assist in improving the prostaglandin metabolism in ischemic heart disease patients.

From the Department of Internal Medicine, National Defense Medical College, Tokorozawa, Saitama, Japan.

* Department of Biochemistry, Nippon Medical School, Tokyo.

Address for reprints: Akira Kurita, M.D., Department of Internal Medicine, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359, Japan.

The paper was partly presented at the 37th Annual Meeting of the American College of Cardiology at Atlanta, Georgia in 1988.

Received for publication April 13, 1989.

Accepted November 8, 1989.

Additional Indexing Words:

Nisoldipine Prostaglandin metabolism Ischemic heart disease

SEVERAL recent studies have shown that slow channel blocking drugs, which are effective in the management of obstructive and vasospastic coronary artery disease, are also efficacious in inhibiting platelet aggregation.¹⁾⁻⁵⁾ Typical slow channel blocking drugs, such as nifedipine and verapamil, inhibit the secondary (TXA₂-dependent) wave of ADP-induced platelet aggregation and appear to have beneficial effects on prostaglandin metabolism in the event of myocardial ischemia.⁶⁾

Nisoldipine, a new calcium channel blocker, is a dihydropyridine derivative that is structurally similar to nifedipine (Fig. 1). It has stronger systemic and coronary hemodynamic effects⁷⁾⁻⁹⁾ than other dihydropyridines, but it may also have a potent effect on prostaglandin metabolites. Although an intravenous infusion of nisoldipine has been shown to increase the myocardial supply in excess of demand,¹⁰⁾⁻¹²⁾ only a few studies have examined its effects on prostaglandin metabolism after either intravenous or oral administration. This study investigated the effects of a low, oral dose of nisoldipine on systemic and coronary hemodynamics, and on prostaglandin metabolism in patients

Table I. Summary of the Effects of Nisoldipine (5mg oral dose) with Chronic, Stable Angina Pectoris

	Pts	Rest	Rest (N)	Sub-E
HR	10	63±11	70±14	84±8
BPs	10	165±23	151±20**	187±25
BPd	10	86±15	82±15	96±18
PRP	10	104±26	101±27	158±30
ST	10			
CSPm	10	7.4±4	4.9±5*	10±5
CSF	10	84±32	109±45	129±48
CVR	10	1.5±0.7	1.0±0.7*	1.1±0.3
MVO ₂	8	9.5±4	10.3±4	
TXB ₂ (A)	10	516±235	516±159	
TXB ₂ (CS)	10	770±417	477±200*	
6KPGF _{1α} (A)	10	414±128	463±141	
6KPGF _{1α} (CS)	10	442±181	396±106	
TXB ₂ /6KPGF _{1α} (A)	10	1.3±0.6	1.2±0.4	
TXB ₂ /6KPGF _{1α} (CS)	10	2.2±0.4	1.2±0.4	

Each value represents the mean±SD. N=post nisoldipine; Sub-E=submaximum of exercise; Max-E=maximum of exercise; Post 5'=post 5 min of exercise; HR=heart rate (bpm); BPs=systolic blood pressure (mmHg); BPd=diastolic blood pressure (mmHg); PRP=pressure rate product (mmHg/bpm·10²); CSPm=mean coronary sinus pressure (mmHg); CSF=coronary sinus

Fig. 1. Chemical structures of the dihydropyridine derivatives, nifedipine and nisoldipine.

with chronic, stable angina pectoris. The rationale for this study was that low, oral doses of the medication would be both economically and physiologically beneficial. Further, a deeper knowledge of the effects of nisoldipine on the prostaglandin metabolites is desired, for they are known to play an important role in the pathogenesis of ischemic heart disease (IHD).¹³⁾⁻¹⁵⁾

on the Hemodynamics and the Prostaglandin Metabolism of Patients
at Rest, During and After Exercise

Sub-E (N)	Max-E	Max-E (N)	Post 5'	Post 5' (N)
87±10	110±16	112±19	72±16	81±21*
172±21**	216±25	202±18**	162±21	152±25*
89±17**	98±18	93±16	82±10	78±12
151±27	233±48	224±52*	118±33	124±46
	4.3±4	2.7±1.6*		
6.1±5*	11.4±7	6.5±5**	7±5	5.4±4
148±40	210±112	226±94		
0.9±0.3	0.8±0.3	0.6±0.3*		
	20±8	20±9		
	585±185	585±171		
	1133±907	720±379*		
	465±135	559±167*		
	447±146	469±134		
	1.3±0.5	1.1±0.5*		
	2.5±1.6	2.5±0.2		

flow (ml/min); CVR=coronary vascular resistance (mmHg/ml/min); $\dot{M}\dot{V}O_2$ =myocardial oxygen content (mlO₂/min); TXB₂=thromboxane B₂ (pg/ml); 6KPGF_{1α}=6 keto-prostaglandin F_{1α} (pg/ml); A=arterial blood; CS=coronary sinus blood. * <0.05, ** <0.01 vs premedication.

METHODS

Selection of patients:

Patients with a predominant history of angina while at rest or an ST segment elevation during episodes of chest pain were excluded from this study. Similarly, patients with severe hypertension, a valvular heart disease, signs of congestive heart failure, intraventricular conduction disturbances, or any other condition likely to influence the ST segment "at rest" were also excluded.

Ten patients, ranging in age from 44 to 65 (mean age: 50), with stable angina pectoris were tested. All had reproducible, exercise-induced angina, associated with horizontal or downsloping ST segment depression of 0.1 mV or more for at least 80 msec after the J point of the baseline of a treadmill test. Each had had at least one fixed coronary artery stenosis (a 70% or greater narrowing of the luminal diameter), determined by routine coronary arteriography. The left ventricular contraction was normal in 8 patients, while the remaining 2 showed hypokinesis.

Beta blockers, calcium blocking drugs, or any other agents that might affect the exercise data were discontinued 14 days prior to the start of the exercise regimen. Platelet-inhibitory drugs, such as aspirin, sulfapyrazone or other agents affecting the prostaglandin release, were also discontinued 7 days prior to testing. Finally, patients did not receive any nitrates except sublingual nitroglycerin within 6 hours of testing.

The test procedure:

All selected patients underwent a graded, supine bicycle exercise test devised by Minjhart. The exercise was started at 50 watts, with the work load being increased 25 watts every 3 min up to each patient's optimal work load. The exercise was terminated on complaint of a chest pain or on observation of a 0.1 mV ST segment depression, with horizontal or downsloping patterns, for 80 msec from the J point. Individual exercise thresholds had been determined at least 90 min prior to the start of exercise and patients underwent their predetermined work loads.

Measurements were taken in the following manner. Under local anesthesia, a sheath was inserted into an antecubital vein, through which a 7 Fr thermodilution catheter (Wilton Lab.) was inserted and positioned in the mid-coronary sinus (CS). The positioning of the catheter was then carefully checked by fluoroscopy. The coronary sinus blood flow (CSF) was measured and calculated by the method described by Ganz et al.¹⁶⁾ A 4 Fr wedge catheter was introduced into the antecubital vein of the opposite arm and

positioned in the mid-CS to measure the CS pressure. The brachial arterial pressure was obtained through a 21-gauge, 5.5 cm teflon needle inserted into the brachial artery. All hemodynamic data were recorded with an 8-channel recorder (Hewlett-Packard 1840). An Acudynamic apparatus was used¹⁷⁾ to obtain the brachial artery and the CS pressures precisely. A three-lead electrocardiogram was taken continuously during the regimen, using a Marquette Case I system, and the ST integral in both aV_F and V_5 was obtained by a 9801 F and PIAS-1 analyzing system (NEC, Tokyo) and was expressed in $\mu\text{v}\cdot\text{sec}$.¹⁸⁾

Measurements at rest were taken after all hemodynamic parameters had stabilized for at least 5 min. As soon as the hemodynamics and CSF were recorded and the blood samples were collected, exercise testing of each patient was performed until the predetermined threshold was reached. When the initial testing was concluded, patients were given 5 mg of nisoldipine orally. Ninety minutes later, after the hemodynamics and CSF were recorded and blood samples collected, the second exercise phase with the same work load was then started. Under this exercise regimen, the effects of nisoldipine on the hemodynamics while at rest, at the middle, and at peak of exercise, as well as at 5 min after the end of exercise were later compared. Similarly, the effects of nisoldipine on the CSF were measured at rest and immediately after exercise.

Calculations and blood sample collection:

The brachial arterial systolic and diastolic pressures were measured every 3 min and a mean value for 10 beats was recorded. The pressure rate product was obtained by calculating heart rate multiplied by the systolic pressure and expressed as $\text{mmHg}/\text{bpm}\cdot 10^2$. The CVR was calculated as the CSF divided by the mean arterial pressure and expressed in $\text{mmHg}/\text{ml}/\text{min}$.

Blood specimens were collected before and immediately after the exercise testing. The first ml of blood was discarded and approximately 10 ml of both the arterial and CS blood were used. The blood samples were mixed and immediately chilled for 30 min before centrifugation at 2,000 g for 20 min at 4°C. The level of TXB_2 was measured by a radioimmunoassay (RIA) of 7 ml blood in 0.5 ml of 4.5 mM EDTA and 1 mM of an acetylsalicylic acid solution to prevent an 'in vitro' breakdown of the arachidonic acid and prostaglandin release. The ^3H -standard TXB_2 and its antibody were obtained from a commercial source (New England Nuclear, Boston, Ma). The $6\text{KPGF}_{1\alpha}$ was measured as a stable product of prostacyclin by RIA, using a standard antibody to $6\text{KPGF}_{1\alpha}$ (New England Nuclear). Measurements of TXB_2 and $6\text{KPGF}_{1\alpha}$ were performed according to a method described by

Kawahara et al¹⁹⁾ and the normal values were 320 ± 13 pg/ml and 414 ± 49 pg/ml, respectively. The reproducibility of the assay for a duplicate determination by the double blind method was 94.4% and the coefficient of the variation of the same sample was between 8 to 17%. Our normal values for TXB₂ and 6KPGF_{1 α} were comparable to RIA results previously reported in the literature.^{20)–22)}

The oxygen content and capacity were determined by manometric analysis and the global myocardial oxygen consumption was derived in the following manner: the arterial O₂ content minus the CS O₂ content times the CSF times 10². The plasma nisoldipine levels were obtained by liquid chromatography and all results are presented in means $\pm$ SD. The statistical analysis of the at rest and exercise variables were calculated using the Student's t-test.

RESULTS

No adverse side effects appeared after the oral intake of 5 mg of nisoldipine. The mean serum nisoldipine level was 3.8 ± 3.1 ng/ml after approximately 90 min.

Effects of nisoldipine while at rest:

Nisoldipine produced an increment in the heart rate and a significant fall in the systolic arterial pressure (prior medication, 165 ± 23 ; post, 151 ± 20 mmHg; $p < 0.01$), though the diastolic arterial pressure and pressure rate product did not change significantly. The mean CSP decreased significantly (prior, 7.4 ± 4 ; post, 4.9 ± 5 mmHg; $p < 0.05$). The CSF increased (prior, 84 ± 32 ; post, 109 ± 45 ml/min; $p < 0.05$) and the coronary vascular resistance (CVR) dropped significantly (prior, 1.5 ± 0.7 ; post, 1.0 ± 0.7 mmHg/ml/min; $p < 0.05$).

The myocardial oxygen consumption presented similar values prior and post medication. The TXB₂ in the brachial artery remained unchanged, whereas the TXB₂ in the CS blood decreased significantly. However, the 6KPGF_{1 α} in the brachial artery and the TXB₂/6KPGF_{1 α} ratio were not significantly affected by nisoldipine.

Effects of nisoldipine during exercise:

The hemodynamic and metabolic effects of the medication were compared at the time of exercise. The ingestion of nisoldipine did not provoke angina attacks. Further, the ST segment integral was significantly reduced (prior medication, 4.3 ± 4 ; post, 2.7 ± 1.6 μ v-sec; $p < 0.05$). The heart

rate did not change appreciably either at the submaximum or at the maximum of exercise. The heart rate, however, was significantly elevated 5 min after exercise. Although the systolic arterial pressure decreased significantly throughout the testing, the diastolic arterial pressure was unaffected.

The pressure rate product decreased at the maximum of exercise (prior, 233 ± 48 ; post, 224 ± 52 mmHg/bpm $\cdot 10^3$; $p < 0.05$) and the mean CS pressure decreased significantly at both the submaximum and the maximum exercise levels. The CSF was unaffected, but the CVR was reduced (prior, 0.8 ± 0.3 ; post, 0.6 ± 0.3 mmHg/ml/min; $p < 0.05$). Further, the TXB₂ level decreased significantly in the CS blood (prior, 1133 ± 907 ; post, 720 ± 379 pg/ml; $p < 0.05$). Finally, the 6KPGF_{1 α} level in brachial artery blood increased (prior, 465 ± 135 ; post, 559 ± 167 pg/ml; $p < 0.05$), whereas the TXB₂/6KPGF_{1 α} in the CS was not reduced significantly.

DISCUSSION

Systemic and coronary hemodynamics:

Ninety minutes after ingestion of 5 mg of nisoldipine, the concentration in plasma was found to be 3.8 ± 3.1 ng/ml. This is a rather low level, compared to the effect of higher ingested doses (10 or 20 mg). A study regarding the effect of the drug in Japanese patients has shown that, 1 hr after an oral 10 mg or 20 mg dose, the plasma concentration peak values are 6.0 ± 3.6 ng/ml and 14 ± 3.8 ng/ml, respectively.²³⁾ There are no other reports regarding plasma concentration levels from 5 mg doses. Even at this low blood concentration, however, nisoldipine was shown to have some effect. The systolic arterial pressure and the CVR were reduced and the CSF increased significantly, but the increment in the heart rate was not remarkable.

During exercise, given the same work load, the systolic arterial pressure and the ST segment were reduced significantly by low-dose nisoldipine therapy. The mean CS pressure also was reduced without apparently affecting the diastolic pressure. Since the coronary perfusion pressure is regulated by the diastolic artery and the coronary sinus-pressure,²⁴⁾ our data suggest that nisoldipine can increase perfusion of the myocardium. Moreover, the increment in the pressure rate product, an indirect result of the myocardial oxygen demand, was reduced during the second exercise regimen. Thus, after the oral dose of nisoldipine, the exercise was performed with less of a myocardial oxygen demand.

Similar results were observed by Lam et al,²⁵⁾ who compared the effects of nisoldipine in exercise testing by utilizing the drug and a placebo in a double-blind test. Cream et al²⁶⁾ also have reported that a 5 mg oral dose

of nisoldipine did not change the heart rate or the systolic arterial pressure appreciably. Further, they found that the exercise time could be prolonged with no change in the summed ST segment depressions, and that a stepwise improvement occurred in extending the exercise parameters with increments in the dosage from 5 to 20 mg. Our observation of an improvement with only a 5 mg dose may be explained by the physique of the average Japanese, who has a thinner skin and is smaller than the average Caucasian.²⁷⁾ Thus, our dosage was sufficient to improve the exercise hemodynamic parameters.

Hemodynamic data indicated that nisoldipine increased the CSF by 29% and reduced the CVR by 33% while at rest. After medication, the CVR was also reduced by 25% during exercise. There have been no previous reports about the effects from 5 mg oral doses of nisoldipine on coronary hemodynamics. An increment in the CSF by an intravenous administration of nisoldipine, though, has been confirmed by Soward et al¹⁰⁾ and Serruys et al,¹¹⁾ who reported an increase of 21 to 31%; they also observed a significant reduction in the CVR. Similarly, our results suggest that an oral dose improves coronary hemodynamics.

When measuring the CSF by the thermodilution technique, the positioning of the catheter is crucial. According to Magorien et al,²⁸⁾ the correlation of consecutive values of the CSF, obtained from measurements by this technique, revealed coefficients of 0.94 at rest, and 0.93 during exercise. For our measurements, we carefully monitored the position of the catheter tip by fluoroscopy. This procedure ensured that the proper catheter position was maintained, so that the CSF values we obtained were reliable throughout exercise testing.

Prostaglandin metabolism:

The effects of nisoldipine on prostaglandin metabolism were also investigated because recent studies indicate that it plays an important role in the pathogenesis of myocardial ischemia.¹³⁾⁻¹⁵⁾ Dusting et al¹³⁾ have proposed a new, homeostatic mechanism in the maintenance of a normal CSF, dependent on the balance among the proaggregative vasoconstrictor, the TXA_2 formed by activate platelets, and the antiaggregative vasodilator prostacyclin, which is produced by the vascular endothelium. To test this hypothesis, we studied the effects of nisoldipine on the TXB_2 and $6\text{KPGF}_{1\alpha}$ levels in both the arterial and CS blood before and immediately after the exercise regimen. Since nisoldipine is structurally similar to nifedipine and has been reported to have a stronger vasodilative effect,⁷⁾⁻⁹⁾ these studies tested for an effect nisoldipine in the formation of TXB_2 or in the production of $6\text{KPGF}_{1\alpha}$.

Our results have revealed that nisoldipine reduced the TXB_2 in the blood of the coronary sinus more markedly than in the blood of the artery. The TXB_2 level in the coronary sinus blood was reduced by 38% at rest, and by 36% during exercise, whereas there was no apparent change in the arterial blood. Since the blood of the coronary sinus received about 94% of the coronary artery inflow,²⁹⁾ our results suggest that the myocardium may be perfused with blood that has a lower affinity for aggregation, which would provide a beneficial effect to the ischemic myocardium.

Nisoldipine also increased the $6\text{KPGF}_{1\alpha}$ in the arterial blood by 11% at rest and by 20% during exercise. Accordingly, nisoldipine reduced the $\text{TXB}_2/6\text{KPGF}_{1\alpha}$ in the arterial blood by 11% and also reduced the ratio in the CS blood by 17% during exercise. This suggests a slight improvement of prostaglandin metabolism. The mechanisms of action of dihydropyridine derivatives are uncertain. However, these effects on prostaglandin metabolism, both in the artery and coronary sinus blood suggest that nisoldipine exerts either a primary beneficial effect on prostaglandin metabolism, or a secondary effect due to the coronary or systemic hemodynamics.

Previous studies^{5),6),30)} have demonstrated that diltiazem inhibits ADP, collagen, and the arachidonate acid-induced platelet aggregation and release, and that verapamil and nifedipine are capable of inhibiting epinephrine-induced platelet aggregation and the TXB_2 release from platelets challenged with epinephrine. Schrör et al³¹⁾ have also reported that 10 mg of nisoldipine inhibited platelet aggregation and thromboxane formation in healthy men after high doses of collagen, which may be related to an increased resistance in the platelet membrane against foreign stimuli. Further, Johnson et al³²⁾ have reported that dihydropyridines are competitive antagonists of the $\text{TXA}_2\text{-PGH}_2$ receptor. However, the precise mechanism involved in these effects at the level of either platelet $\text{TXA}_2\text{-PGH}_2$ receptors or vascular $\text{TXA}_2\text{-PGH}_2$ receptors is uncertain.

In conclusion, nisoldipine may improve prostaglandin metabolism by either inhibiting the formation of TXB_2 , or facilitating the production of prostacyclin in the vessel wall. These effects may be related to a primary or secondary improvement in the systemic or coronary hemodynamics. Although further study is required to determine whether nisoldipine has a beneficial homeostatic effect on the metabolism during myocardial ischemia, our results have demonstrated that even a low, oral dose of nisoldipine moderately affects the systemic and coronary hemodynamics and assists in improving the prostaglandin metabolism in IHD patients.

ACKNOWLEDGMENTS

The authors would like to thank Mr. Joseph A. Grace for his help in reading this manuscript.

REFERENCES

1. Addonizio VP, Fisher CA, Edmunds LH: Effects of verapamil and nifedipine on platelet activation. *Circulation* **62** (suppl III): 326, 1980
2. Ikeda Y, Kikuchi M, Toyama K, Watanabe K, Ando Y: Inhibition of human platelet functions by verapamil. *Thromb Haemost* **45** (suppl 2): 158, 1981
3. Burns ER, Frishman WH: The antiplatelet effects of calcium channel blockers add to their antianginal properties. *Int J Cardiol* **4**: 372, 1983
4. Chierchia S, Crea F, Bernini W, Gensini G, Parodi O, De Caterina R, Maseri A: Antiplatelet effects of verapamil in man. *Am J Cardiol* **47**: 399, 1981
5. Ono H, Kimura M: Effects of Ca^{2+} -antagonistic vasodilators, diltiazem, nifedipine, perhexiline and verapamil, on platelet aggregation in vitro. *Arzneim Forsch* **31**: 1131, 1981
6. Johnson GJ, Leis LA, Francis GS: Disparate effects of the calcium-channel blockers, nifedipine and verapamil, on α_2 -adrenergic receptors and thromboxane A_2 -induced aggregation of human platelets. *Circulation* **73**: 847, 1986
7. Kazda S, Garhoff B, Meyer H: Pharmacology of a new calcium antagonistic compound isobutyl methyl 1,4 dihydro-2, 6-dimethyl-4-(2-nitrophenyl)-3,5-purinedicarboxylate (nisoldipine, Bay k 5552). *Arzneim Forsch* **30**: 2144, 1980
8. Warltier DC, Meila CM, Gross GJ, Brooks HL: Blood flow in normal and ischemic myocardium after verapamil, diltiazem and nisoldipine (Bay k 5552), a new dihydropyridine calcium antagonist. *J Pharmacol Exp Therap* **218**: 296, 1981
9. Vogt A, Neuholds KL, Krenzer H: Hemodynamic effects of the new vasodilator drug Bay k 5552 in man. *Arzneim Forsch* **30**: 2162, 1980
10. Soward AL, Feyter PJD, Hugenholtz PG, Serruys PW: Maintenance of increased coronary blood flow in excess of demand by nisoldipine administered as an intravenous infusion. *Am J Cardiol* **58**: 1199, 1986
11. Serruys PW, Suryapanta H, Planellas J, Wijns W, Vanhaleweyck LJ, Soward AL, Jaski BE, Hugenholtz PG: Acute effects of intravenous nisoldipine on left ventricular function and coronary hemodynamics. *Am J Cardiol* **56**: 140, 1985
12. Roussau MF, Vincent MF, Hoof FV, Bergha VD, Charlier AA, Pouleur H: Effects of nicardipine and nisoldipine on myocardial metabolism, coronary blood flow and oxygen supply in angina pectoris. *Am J Cardiol* **54**: 1189, 1984
13. Dusting GJ, Moncada S, Vane JR: Prostaglandins, their intermediates and precursors: Cardiovascular actions and regulatory roles in normal and abnormal circulatory systems. *Prog Cardiovasc Dis* **21**: 405, 1979
14. Hirsh PD, Hillis LD, Campbell WB, Firth BG, Willerson JT: Release of prostaglandins and thromboxane into the coronary circulation in patients with ischemic heart disease. *New Engl J Med* **304**: 685, 1981
15. Vane JR: Prostaglandin and cardiovascular system. *Br Heart J* **49**: 405, 1983
16. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC: Measurement of coronary sinus blood flow by continuous thermodilution in man. *Circulation* **44**: 189, 1971
17. Garner RM: Direct blood flow pressure measurement-dynamic response requirement. *Anesthesiology* **54**: 227, 1981
18. Sheffield LT, Holt JT, Laster FM, Conroy DV, Reeves AJ: On-line analysis of the exercise electrocardiogram. *Circulation* **40**: 935, 1969
19. Kawahara K, Sugita H, Masanori O, Takata N: A simple, rapid and simultaneous extrac-

- tion of thromboxane B_2 6 keto-prostaglandin $F_{1\alpha}$ and prostaglandin E_2 . *Jpn J Inflammation* **7**: 511, 1987
20. Metha J, Metha P, Feldman RL, Horalek C: Thromboxane release in coronary artery disease: spontaneous versus pacing-induced angina. *Am Heart J* **107**: 286, 1984
 21. Tada M, Kuzuya T, Inoue M, Kodama K, Mishima M, Yamada M, Inui M, Abe H: Elevation of thromboxane B_2 levels in patients with classic and variant angina pectoris. *Circulation* **64**: 1107, 1981
 22. Morris HG, Sherman NA, Shepperdson FT: Variable associated with radioimmunoassay of prostaglandins in plasma. *Prostaglandins* **21**: 771, 1981
 23. Iimura H, Kato K: Bay k 5552 Phase I study. *Clinical Report* **22**: 29, 1988
 24. Marcus ML: *The Coronary Circulation in Health and Disease*, McGraw-Hill, New York, p 93, 1983
 25. Lam J, Chaitman BR, Crean PA, Blum R, Waters DD: A dose-ranging, placebo-controlled, double-blind trial of nisoldipine in effort angina. Duration and extent of antianginal effects. *J Am Coll Cardiol* **6**: 447, 1986
 26. Crean PA, Waters DD, Lam J, Chaitman BR: Comparative antianginal effects of nisoldipine and nifedipine in patients with chronic stable angina. *Am Heart J* **113**: 261, 1987
 27. Key A: Coronary heart disease in seven countries. Relative body weight. *Circulation* **41** (suppl I): I-199, 1968
 28. Magorien RD, Friederick J, Lefer CV, Chaitman BR: Influence of exercise on coronary sinus blood flow determinations. *Am J Cardiol* **50**: 659, 1987
 29. Hood WB: Regional venous drainage of the human heart. *Br Heart J* **30**: 105, 1968
 30. Shino A, Sasaki Y, Inamaso M: In vitro effects of the coronary vasodilator diltiazem on human and rat platelets. *Thromb Res* **13**: 941, 1978
 31. Schrör K, Latta G, Darius H, Klaus W, Ziegler R: Hemmung der plättchenaggregation und thromboxanbildung durch calcium-antagonisten nisoldipine nach einer oralen einmal dosis von 10 mg. *Klin Wochenschr* **63**: 16, 1985
 32. Johnson GJ, Dunlop PC, Leis LA: From dihydropyridine agonist Bay k 8664 inhibits platelet activation by competitive antagonism of thromboxane A_2 -prostaglandin H_2 receptor. *Circ Res* **62**: 494, 1988