The Effect of Dipyridamole on the Coronary Hemodynamics in Man

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SUMMARY

The effects of Dipyridamole (Persantin) on the coronary blood flow (the great cardiac vein flow and coronary sinus ostial flow), the femoral arterial pressure, the coronary vascular resistance and the heart rate were measured continuously in man.

The newly devised method of the continuous local thermodilution method enabled us to perform the exact measurement of the above mentioned variables in man.

The increase of the coronary blood flow was seen definitely in the non-ischemic group and, therefore, the decrease in the coronary vascular resistance occurred in 30 sec and continued for more than 20 min. In the myocardial ischemic group, some patients showed the similar response to the non-ischemic group. However, some patients showed no increase of the flow, even though the coronary vascular resistance decreased in all cases in this group. The heart rate increased slightly in all cases.

Additional Indexing Words:

Dipyridamole Coronary blood flow

THE data that Dipyridamole increases the coronary blood flow in the animals have been reproducible and well accepted.^{1),2)} However, because of the technical difficulties in the clinical medicine, the direct proof in man that Dipyridamole increases the coronary blood flow and decreases the coronary vascular resistance is poor and incomplete.³⁾⁻¹¹⁾

Since we developed the new method for the continuous measurement of the coronary sinus blood flow in man,¹²⁾ an attempt to prove the increase of the coronary blood flow by Dipyridamole in man became possible. Therefore, the object of this study was to examine the changes of the coronary blood flow and the coronary vascular resistance in man after Dipyridamole continuously using this newly developed local thermodilution method.

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MATERIAL AND METHOD

The 14 patients under the usual cardiac catheterization studies were selected randomly for this clinical experiment (Table I). This study was performed immediately after the usual catheterization. The patients were classified into 2 groups, namely (A) the myocardial non-ischemic group as the control and (B) the myocardial ischemic group. The criteria of the myocardial ischemia were the followings: (1) the inpatients due to the acute myocardial infarction with the definite electrocardiographic and enzymatic changes, (2) the patients of angina pectoris in whom the spontaneous attacks showed the transient and reversible horizontal depression of the ST segment in the electrocardiogram and the attacks were relieved by nitroglycerin. The patients without the myocardial ischemia criteria were classified as the myocardial non-ischemic group. In order to correlate the reaction of the coronary blood flow to Dipyridamole, with each patient, the clinical manifestations and the laboratory findings of each patient were summarized in Table I.

The patients were premedicated by morphine HCl (10 mg) and phenobarbital (20 mg) intramuscularly.

The simultaneous measurements of the flow in the great cardiac vein and the coronary sinus were performed by the newly developed method of the continuous local thermodilution method.¹²⁾ A specially designed catheter (equivalent 7F) (Wilton Webster Manufacturing Company, USA) was inserted into the coronary sinus. This catheter has the injection orifice at the top of it and the 3 thermistors. The 2 external thermistors were mounted outside of the catheter, namely 10 mm (great cardiac vein) and 30 mm (coronary sinus) and the 1 thermistor was mounted inside the catheter to measure the temperature of the indicator. The temperature was measured with the thermistors incorporated in one arm of a Wheatstone bridge, the signal was amplified and recorded by the photorecorder (Yokogawa, Type 2902) continuously. The 5% glucose solution was infused continuously by a specially designed infusion pump through the small hole at the tip of the catheter into the great cardiac vein for the mixing. The temperature of the blood, the mixture of the blood, and the indicator were measured by the external thermistors. The flows were converted from the changes of the temperature of the mixture of the blood and the indicator according to the formula that was already reported.¹²⁾

After 30 sec of the infusion of the indicator, the flow became stable and Dipyridamole (10 mg) was injected intravenously in a single shot. The changes of the flow after Dipyridamole were recorded continuously.

The Seldinger needle of G17 was inserted into the femoral artery to record the changes of the mean arterial pressure. The coronary vascular resistance was calculated by the mean arterial pressure divided by either the great cardiac vein flow or the coronary sinus ostial flow. Moreover, the morphologies and the rhythm changes in the electrocardiogram were also analysed during the procedure.

RESULTS

The data of the effects of Dipyridamole on the coronary hemodynamics

Table I. The Clinical Manifestations and the Laboratory Findings
of the Patients Examined in This Study

A. Myocardial Non-Ischemic Group

Case No.	Name & Age	Sex	Body Surface (M ²)	Clinical Diagnosis	BP mmHg	ECG Findings
						At Rest
1	K. O. 55	M	1.56	Aortic insufficiency	158/80	SV ₁ +RV ₅ =40 mm L _{1,2} , V _{4,5,6} ST depression
2	S. S. 30	M	1.60	Aortic insufficiency, Chronic glomerulonephritis	180/30/0	SV ₁ +RV ₅ =70 mm No ST depression
3	S. A. 33	M	1.71	Innocent murmur	120/80	Normal (SV ₁ +RV ₅ =28 mm)
4	M. S. 21	M	1.72	Myocardiopathy	106/68	SV ₁ +RV ₅ =45 mm STV _{5,6} : depressed STV _{1,2} : elevated TV ₄₋₆ : negative
5	A. K. 50	F	1.30	Thromboembolism of both ext. iliac Vs.	112/60	SV ₁ +RV ₅ =41 mm
6	K. E. 52	M	1.62	Mitral stenosis	140/88	Atrial fibrillation, iRBBB
7	I. S. 28	F	1.38	Aortitis syndrome	154/48	Normal
8	Y. S. 23	F	1.40	Mitral stenosis	108/70	RVH, Mitral P
9	M. K. 39	M	1.62	Mitral stenosis (restenosis)	130/60	Atrial fibrillation, RVH, LVH

Case No.	Name & Age	Sex	Body Surface (M ²)	ECG Findings	Chest X-ray Film Cardio-thoracic Ratio	PCG Findings	Cardiac Catheterization	
				Master's Test			PA Wedge Pressure	RV Diastolic Pressure (mmHg)
1	K. O. 55	M	1.56	—	50.0	4LSB, DM	6.0	5.5
2	S. S. 30	M	1.60	—	72.4	4LSB, DM	24.9	12.1
3	S. A. 33	M	1.71	—	58.3	Innocent SM	8.0	0
4	M. S. 21	M	1.72	—	48.0	Pure	13.9 Normal coronary angiogram	5.3
5	A. K. 50	F	1.30	—	54.8	Pure	—	—
6	K. E. 52	M	1.62	—	50.0	Q-I interval=0.10 sec 5L10, DM, no OS	16.0	5.7
7	I. S. 28	F	1.38	—	50.0	2RSB, SM	9.0	4.5
8	Y. S. 23	F	1.40	—	52.0	5L10, DM, OS	17.0	11.0
9	M. K. 39	M	1.62	—	67.8	5L10, DM, OS	44.0	11.0

Table I. Continued

Case No.	Name & Age	Sex	Body Surface (M ²)	NYHA		Lipid Abnormalities			OGTT	Comments
				Functional	Therapeutic	Plasma Cholesterol (mg/100 ml)	Plasma β -lipoprotein	Plasma Triglyceride		
1	K. O. 55	M	1.56	2°	B	—	—	—	Normal	Onset ; 6 yrs before
2	S. S. 30	M	1.60	2°	B	188	407	—	Normal	8 y.o. ; rheumatic fever
3	S. A. 33	M	1.71	1°	A	202	508	146	Normal	Arrhythmia, occasionally
4	M. S. 21	M	1.72	1°	A	134	281	—	Normal	Since 17 y.o. paroxysmal tightness of chest
5	A. K. 50	F	1.30	1°	A	226	—	—	Normal	23 y.o. ; appendectomy caused thromboembolism
6	K. E. 52	M	1.62	1°	A	150	—	—	Normal	Onset ; 5 yrs before
7	I. S. 28	F	1.38	1°	A	142	457	66	Normal	Onset ; 2.5 yrs before
8	Y. S. 23	F	1.40	2°	B	—	—	—	Normal	Onset ; 12 yrs before
9	M. K. 39	M	1.62	2°	B	185	357	83	Normal	Commisurotomy ; 1 yr before

B. Myocardial Ischemic Group

Case No.	Name & Age	Sex	Body Surface (M ²)	Clinical Diagnosis	BP	ECG Findings
						At Rest
A	M. Y. 43	M	1.64	Myocardial infarction	112/60	Abnormal Q : L ₁ , aV _L , R/S V ₁ > 1, SV ₁ + RV ₅ = 35 mm
B	K. A. 46	F	1.35	Angina pectoris	130/70	SV ₁ + RV ₅ = 28 mm
C	K. K. 65	M	1.62	Angina pectoris	140/34	SV ₁ + RV ₅ = 25 mm
D	K. M. 47	M	1.68	Myocardial infarction	120/80	V ₁₋₄ : QS
E	K. Y. 59	M	1.59	Angina pectoris	150/70	SV ₁ + RV ₅ = 51 mm, aV _L , V _{4,5} ST depression

The patients were classified either in the myocardial non-ischemic group or in the myocardial ischemic group.

PA=pulmonary artery ; RV=right ventricle ; NYHA=New York heart association ; OGTT=oral glucose tolerance test ; M=male ; LSB=left sternal border ; DM=diastolic murmur ; F=female ; iRBBB=incomplete right bundle branch block ; OS=opening snap ; SM=systolic murmur ; RVH=right ventricular hypertrophy ; LVH=left ventricular hypertrophy

Table I. Continued

Case No.	Name & Age	Sex	Body Surface (M ²)	ECG Findings	Chest X-ray Film	Cardiac Catheterization			Functional
				Master's Test	Cardiothoracic Ratio	PCG Findings	PA Wedge Pressure	RV Diastolic Pressure (mmHg)	
A	M. Y. 43	M	1.64	—	53.0	Pure	12.7	4.2	2°
B	K. A. 46	F	1.35	V ₄₋₆ : ST depression	52.0	Innocent SM	8.3	5.5	3°
C	K. K. 65	M	1.62	V ₄₋₆ : ST depression	49.0	Innocent SM	19.0	7.0	2°
D	K. M. 47	M	1.68	—	47.3	Pure	19.0	7.0	2°
E	K. Y. 59	M	1.59	V _{3,4,5} : ST depression	50.0	Innocent SM	17.1	8.0	2°

Case No.	Name & Age	Sex	Body Surface (M ²)	Lipid Abnormalities				OGTT	Comments
				Therapeutic	Plasma Cholesterol (mg/100 ml)	Plasma β -lipoprotein	Plasma Triglyceride		
A	M. Y. 43	M	1.64	C	191	407	54	Normal	Onset; 4 mo before
B	K. A. 46	F	1.35	C	196	281	58	Normal	Onset; 1 yr 8 mo before
C	K. K. 65	M	1.62	C	196	432	58	Normal	Onset; 3 yrs before
D	K. M. 47	M	1.68	C	274	710	177	Normal	Onset; 3 mo before
E	K. Y. 59	M	1.59	B	214	483	122	Normal	Onset; 5-6 yrs before

were summarized in the myocardial non-ischemic group in Table II and in the myocardial ischemic group in Table III. In order to help the understanding, taking the mean and the standard deviation of each variable in Tables II and III, the summary of the effects of Dipyridamole are diagrammatically shown in Fig. 1 and 2.

The great cardiac vein flow (Table II and Fig. 1) increased in all cases in the non-ischemic group after 30 sec of the injection. The peak of the increase of the flow was seen within 2 min after the injection. The magnitude of the increase of the flow was between 20 to 90% of the flow before the injection. The duration of the increased flow was more than 10 min. In the

Table II. The Summary of the Effects of Dipyridamole on the Great Cardiac the Coronary Vascular Resistance, the Heart Rate, the Heart Rate

1. Great Cardiac Vein Flow [ml/min ($\Delta\%$ from pre-injection value)]:

Case No.	Pre.	0.5 (min)	1	1.5	2	3
3	91.4 (100)		123 (135)		108.9 (119)	108.4 (119)
4	88.3 (100)	156.3 (177)	127.8 (145)	127.8 (145)		
5	36.7 (100)	33.5 (91)	44.6 (122)	41.5 (113)		
6	75.1 (100)	115 (153)	108 (145)		74.8 (100)	81.8 (109)
8	86.1 (100)	106 (123)	156 (181)	167 (194)	165 (192)	134 (156)
9	115 (100)	111 (97)	135 (117)	180 (157)		
	100	128.2 $\pm$ 36.7	140.8 $\pm$ 22.8	152.3 $\pm$ 33.5	137.0 $\pm$ 48.6	128.0 $\pm$ 24.8

2. Coronary Sinus Ostial Flow [ml/min ($\Delta\%$ from pre-injection value)]:

1	247 (100)	380 (154)	380 (154)	448 (181)		
2	268 (100)	290 (108)	315 (118)		384 (143)	306 (114)
3	193.8 (100)		232.9 (120)		195.1 (101)	189 (97)
5	328.8 (100)		339.4 (113)	312.3 (95)		
6	105 (100)	133 (127)	135 (129)		100 (105)	109 (104)
7	111 (100)	125 (127)	112 (101)		119 (107)	126 (114)
	100	129.0 $\pm$ 18.9	122.5 $\pm$ 18.0	138.0 $\pm$ 60.8	114.0 $\pm$ 19.5	107.3 $\pm$ 8.3

3. Mean Femoral Arterial Pressure [mmHg ($\Delta\%$ from pre-injection value)]:

4	84 (100)	77 (92)	80 (95)	85 (101)		
5	71 (100)	72 (101)	69 (96)	65 (91)		
6	104 (100)	103 (100)	115 (111)		103 (100)	109 (109)
7	108 (100)	108 (100)	106 (98)		101 (94)	102 (95)
8	66.3 (100)	62.7 (95)	57.3 (86)	55.7 (84)	48.3 (73)	59 (89)
9	102 (100)	96.2 (94)	95.6 (94)	90.1 (88)		
	100	97.0 $\pm$ 3.8	96.7 $\pm$ 8.1	91.0 $\pm$ 7.3	89.0 $\pm$ 14.2	97.0 $\pm$ 10.3

4. Coronary Vascular Resistance [(3)/(1) ($\Delta\%$ from pre-injection value)]:

4	0.95(100)	0.49(62)	0.62(65)	0.67(70)		
5	1.93(100)	2.15(111)	1.55(80)	1.57(81)		
6	1.38(100)	0.90(65)	1.06(70)		1.38(100)	1.38(100)
7	0.97(100)	0.86(89)	0.95(98)		0.85(88)	0.81(84)
8	0.77(100)	0.59(77)	0.37(48)	0.33(43)	0.29(38)	0.44(57)
9	0.89(100)	0.87(98)	0.71(80)	0.50(50)		
	100	83.7 $\pm$ 19.2	74.7 $\pm$ 16.8	61.0 $\pm$ 17.6	75.3 $\pm$ 32.9	80.3 $\pm$ 21.7

Vein Flow, the Coronary Sinus Ostial Flow, the Mean Arterial Blood Pressure,
and the Blood Pressure Product in the Myocardial Non-ischemic Group

4	5	6	7	10	13	16	20
115.3 (131)		104.3 (114)			102.5 (116)		
		41.5 (113)		94.0 (125)			
		99.6 (116)		92.1 (107)			
173 (150)							
140.5±13.4		114.3±1.5		116.0±12.7	116		

							312 (127)
		196.3 (101)	204.5 (106)				
		312.3 (95)		119 (113)			
		120 (108)					
		101.3±6.5	106	113			127

84 (100)		57 (80)			84 (100)	61 (86)	
				107 (103)			
		54.7 (83)		60.0 (91)			
91 (89)				88.9 (87)			
94.5±7.3		81.5±2.1		93.7±8.3	100	86	

0.73(77)		1.26(65)			0.82(86)		
				1.14(83)			
		0.55(71)		0.65(84)			
0.53(60)							
68.5±12.0		68.0±4.2		83.5±0.7	86		

Table II. Continued

5. Heart Rate [/min ($\Delta\%$ from pre-injection value)]:

Case No.	Pre.	0.5 (min)	1	1.5	2	3
1	50 (100)	60 (100)	60 (100)	63 (105)		
2	80 (100)	79 (98)	85 (106)	84 (105)	83 (104)	80 (100)
3	72 (100)		90 (125)		81 (113)	83 (117)
4	57 (100)	60 (105)	60 (105)	60 (105)		
5	68 (100)	68 (100)	68 (100)	72 (106)		
6	104 (100)	103 (100)	115 (111)		103 (100)	113 (109)
7	120 (100)	126 (105)	126 (105)	126 (105)	126 (105)	132 (110)
8	63 (100)	63 (100)	65 (103)	66 (105)	66 (105)	66 (105)
9	81 (100)	81 (100)	87 (107)	90 (111)		
	100	101.0 $\pm$ 2.6	106.9 $\pm$ 7.6	106.0 $\pm$ 2.2	105.4 $\pm$ 4.7	108.2 $\pm$ 6.3

6. Heart Rate $\times$ Mean Femoral Arterial Pressure (beats $\times$ mmHg/min):

4	4788 (100)	4620 (96)	4800 (100)	5100 (107)		
5	4828 (100)	4896 (101)	4692 (97)	4680 (97)		
6	5304 (100)	5562 (105)	6210 (117)		5253 (99)	5886 (111)
7	12960 (100)	13608 (105)	13356 (103)		12726 (98)	13464 (104)
8	4126.9 (100)	3950.1 (95)	3724.5 (89)	3676.2 (88)	3187.8 (76)	3894.0 (93)
9	8262 (100)	7792.2 (94)	8317.2 (101)	8109.0 (98)		
	100	99.3 $\pm$ 5.0	101.2 $\pm$ 9.2	97.5 $\pm$ 7.8	91.0 $\pm$ 7.8	102.7 $\pm$ 9.0

myocardial ischemic group the increase of the flow was seen in some cases in this group similar to the control group. Namely, the peak of the increase of the flow was also seen within 2 min after the injection. The magnitude of the increase of the flow was less than the control group and it was in 20 to 50 % compared to the flow before the injection. The duration of the increase of the flow was longer than 6 min. In the myocardial ischemic group, however, some cases did not show any increase of the flow in contrast to the cases so far described.

The coronary sinus ostial flow (Table II and Fig. 1) increased also in all cases in the myocardial non-ischemic group after Dipyrindamole similar to the response to the great cardiac vein flow. The peak and the duration of the increase of the flow were also similar to the increase in the great cardiac vein flow. In 1 case (case 1) the duration of the increased flow was definitely seen even in the 20 min after the injection. In the myocardial ischemic group (Table III and Fig. 2), the pattern of the increase of the flow was almost similar to the myocardial non-ischemic group. Therefore, the increase of either the great cardiac vein or the coronary sinus ostial flow was definitely

4	5	6	7	10	13	16	20
80 (100)	81 (100)	80 (100)	80 (100)				60 (100)
57 (100)		84 (117)	96 (133)		54 (95)		
				107 (103)			
84 (104)		72 (114)		65 (103)			
				93 (115)			
101.3±2.3	100	110.3±9.6	116.5±23.3	107.0±6.9	95		190

4788 (100)					4536 (95)		
				5136 (97)			
		3938.4 (94)		3900.0 (93)			
7644.0 (93)				8267.7 (100)			
96.5±5.0		84		96.7±3.5	95		

seen in most cases with some exceptions.

The mean femoral arterial pressure (Table II and Fig. 1) in the myocardial non-ischemic group decreased slightly in 5 cases out of 6. The peak of the decrease in the blood pressure was in 2 min, coinciding to the increase of the flow in this same period. In some cases the decrease of the flow was delayed until 6 min, even though the increase of the coronary blood flow was seen in this time. The magnitude of the decrease in the blood pressure was less than 20%. In the myocardial ischemic group (Table III and Fig. 2), the changes of the blood pressure after the injection was less than those of the changes in the myocardial non-ischemic group. Namely, the changes of the blood pressure were almost unrecognizable in the myocardial ischemic group.

The data so far disclosed indicate, in the myocardial non-ischemic group, the increase of the coronary flow and the decrease of the pressure. Therefore, the calculated coronary vascular resistance decreased definitely. The decrease of the coronary vascular resistance was more remarkably seen in the myocardial non-ischemic group than the myocardial ischemic group as shown in the Table II and Fig. 1. Namely, the coronary vascular resistance was

Table III. The Summary of the Effects of Dipyrindamole on the Great Cardiac Vein Flow, the Coronary Sinus Ostial Flow, the Mean Arterial Blood Pressure, the Coronary Vascular Resistance, the Heart Rate, the Heart Rate and the Blood Pressure Product in the Myocardial Ischemic Group

1. Great Cardiac Vein Flow [ml/min ($\Delta\%$ from pre-injection value)]:

Case No.	Prc.	0.5 (min)	1	1.5	2	3	4	5	6
B	72.8 (100)	74.0 (102)	85.8 (118)	85.8 (118)	85.8 (118)	82.1 (98)	101 (139)	84.2 (100)	85.3 (101)
C	84.2 (100)		86.1 (102)		80.8 (96)			106 (114)	108 (116)
D	92.9 (100)	108 (116)	93.9 (101)	89.9 (97)	91.4 (93)	95.0 (98)			
E	117.9 (100)	173.3 (147)	146.5 (124)	178.1 (151)	144.7 (123)	142.1 (121)		145.6 (123)	
	100	121.7 $\pm$ 23.0	111.3 $\pm$ 11.5	122.0 $\pm$ 27.2	107.5 $\pm$ 15.2	105.7 $\pm$ 13.3	139	112.3 $\pm$ 11.6	108.5 $\pm$ 10.6

2. Coronary Sinus Ostial Flow [ml/min ($\Delta\%$ from pre-injection value)]:

A	156.4 (100)		182.0 (116)		182.0 (116)	167.0 (107)			167.0 (107)
E	167.5 (100)	243.4 (145)	178.1 (106)	239.2 (143)	195.7 (117)	181.9 (109)		203.2 (121)	
	100	145	111.7 $\pm$ 7.1	143	116.5 $\pm$ 0.7	108 $\pm$ 1.4		121	107

3. Mean Femoral Arterial Pressure [mmHg ($\Delta\%$ from pre-injection value)]:

A 9	87.4 (100)		86.7 (99)		77 (88)	85.3 (98)			78.7 (90)
B 11	91 (100)	93 (103)	91 (100)		89 (97)				
C 12	104 (100)		104 (100)		103 (99)	103 (99)	105 (101)	100 (96)	100 (96)
D 14	95.3 (100)	96 (101)	96 (101)	96 (101)	96 (101)	100.7 (106)		100 (105)	100 (105)
E 15	123 (100)	123 (100)	117 (95)	117 (95)	118 (96)			117 (95)	
	100	101.3 $\pm$ 1.5	99 $\pm$ 2.4	98 $\pm$ 4.2	96.2 $\pm$ 5.0	101 $\pm$ 4.4	101	98.7 $\pm$ 5.5	97 $\pm$ 7.6

Fig. 1. The summary of the effect of Dipyridamole on the coronary hemodynamics in the myocardial non-ischemic group. The changes were shown in percentage from the value before the injection. The mean and the one standard deviation is shown as the middle bar with the short arms.

definitely decreased even in the myocardial ischemic group (Table III and Fig. 2). The duration of the decrease in the resistance was more than 10 to 13 min.

The heart rate in the myocardial non-ischemic group increased definitely in about 10% in all cases. The increase in the heart rate during this period coincided almost to the increase of the coronary blood flow. This increase

Fig. 2. The summary of the effect of Dipyridamole on the coronary hemodynamics in the myocardial ischemic group. The changes were shown in percentage from the value before the injection of Dipyridamole. The middle bar indicates the mean value and one standard deviation is also indicated as the short bar.

in the heart rate was also seen in the myocardial group.

The rate and the pressure product did not change significantly in the myocardial non-ischemic group because the mean femoral arterial pressure decreased and the heart rate increased slightly. In the myocardial non-

ischemic group, the mean femoral arterial pressure did not change and the heart rate increased slightly. Therefore, the rate and pressure product increased rather slightly in this group.

DISCUSSION

The experimental pharmacological effect of Dipyridamole in the animals has been reported as follows: (1) Dipyridamole increases the myocardial blood flow.²⁾ Therefore, it boost the development of the formation of the collateral channels in the myocardial ischemic area.¹³⁾ (2) It improves the myocardial metabolism by the better utilization of the myocardial oxygen. (3) It shows the positive inotropic effect resulting in the improvement in the myocardial contractility.⁸⁾

The evaluation of these effects of Dipyridamole directly in man is quite difficult in the clinical medicine. However, we developed the new method for the measurement of the coronary blood flow continuously in man by the continuous local thermodilution method.¹²⁾ This new method enabled us to measure the effect of Dipyridamole especially on the coronary blood flow in man. This project has not been completed as a whole, because the effect of Dipyridamole in animals disclosed the above mentioned 3 items, and these items should be clarified in man. The data so far completed disclosed the effect of the item (1) which was described in the animal experiment.

Because there was no method of the continuous measurement of the coronary blood flow in man, there has been reported no direct proof that Dipyridamole increases the coronary blood flow in man continuously. This is the first report of the continuous measurement of the coronary blood flow in man. Even by the nitrous oxide method, practically the flow was able to be measured in every 10 min. Wendt and Bing⁶⁾ showed the increase of the coronary blood flow by the nitrous oxide method. The 8 cases out of 9 showed the increase of the flow of 18% in average. The coronary vascular resistance, therefore, decreased. The rest of the reports proved the increase of the coronary blood flow indirectly by measuring the oxygen content in the coronary sinus. Kinsella and McGregor³⁾ reported the increase of the coronary blood flow even in the presence of the severe coronary heart disease. They gave 20 mg of Dipyridamole intravenously and measured the oxygen in the coronary sinus in 2, 5, 10, and 30 min. Bernsmeier⁴⁾ measured also oxygen in the coronary sinus and showed the increase of about 10% by Dipyridamole of 0.2 mg/Kg given intravenously. The effect disappeared in 15 min. Therefore, he doubted the effectiveness of Dipyridamole. Peel⁵⁾ injected Dipyridamole (0.16 to 0.30 mg/Kg) intravenously in the patients of mitral stenosis. The

oxygen in the coronary sinus increased from 7 to 36 %. Knipping⁸⁾ gave 20 mg of Dipyridamole in 20 patients and showed the increase of the oxygen in the coronary sinus in 5 min. Schollmeyer⁸⁾ measured also the oxygen in the coronary sinus in the myocardial non-ischemic patient after injection of Dipyridamole (0.4 to 0.8 mg/Kg in 2 min). The oxygen in the coronary sinus increased in 3 min and the increase continued for more than 60 min. He also noted the increase of the frequency of the heart rate. The blood pressure changes were not noted. Hilgar⁹⁾ also showed the similar results. Doll¹⁰⁾ clarified the increase of the arteriovenous oxygen difference after Dipyridamole. Rudolph¹¹⁾ showed the transient increase in the coronary blood flow of about 10 % after Dipyridamole (0.2 to 0.4 mg/Kg). Therefore, he concluded that Dipyridamole is not effective in acute disturbances of the coronary circulation.

In this study, the continuous measurement of the coronary blood flow in man showed that the coronary blood flow increased definitely in the myocardial non-ischemic group. In the myocardial ischemic group, some patients showed the increase of the flow and some other patients showed no increase of the flow. According to the clinical manifestations and the laboratory findings, these differences in the response to the drug would be based upon the pathologic changes of the coronary arteries and the existence of the myocardial ischemia. The increase of the coronary blood flow was quite similar to the reports such as described already. However, the magnitude, the time of peak and the duration of the increased flow were well disclosed by this study.

It is therefore quite possible that Dipyridamole increases the coronary blood flow in most of the myocardial ischemic patients and improves the myocardial efficiency.¹³⁾ However, the increase of the coronary blood flow does not mean the improvement of the myocardial ischemia, because the increased flow might be shunted away from the ischemic area. The attempt to assess the long-term effects attributable to Dipyridamole has been reported by Mason et al.¹³⁾ Their data showed that Dipyridamole can favorably influence the development of intercoronary anastomosis when administered over the long term. The other question which should be answered is that in some patients of myocardial ischemia there was no increase of the coronary blood flow and so how is Dipyridamole effective to such a patient. The study such as Mason et al.¹³⁾ might answer to this question in future. We also have attempted to measure the myocardial metabolic changes such as the reversal of the lactate production by the anaerobic metabolism in the myocardium. Therefore, it is quite possible that Dipyridamole, acting as the coronary vasodilator, increases the coronary flow and might boost the formation of the collateral channels in most of the patients even with moderate myocardial ischemia. However, some patients with diffuse myocardial ischemic changes did not show

the increase of the coronary blood flow. The effectiveness of Dipyridamole even to such patients will require further study by certifying the improvement of the myocardial ischemic metabolism directly in man.

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