The Effect of Coronary Vasodilators on the Coronary Circulation and the Myocardial Metabolism in the Sclerotic Heart Diseases

YOSHIO ITO, YOSHIYASU HASEGAWA

*The Department of Internal Medicine, Tokyo University Branch Hospital, Tokyo
(Director: Prof. Tachio Kobayashi)*

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THERE ARE MANY coronary vasodilators now in hand of the physician for clinical use. Nevertheless the studies of their effects on the coronary circulation and/or myocardial metabolism in the ischaemic heart diseases are scarce, except for the reports given by Gorlin¹⁾ and others^{2)~6)}.

It is the purpose of this communication to describe the hemodynamic and metabolic changes of hearts after the use of various coronary vasodilators in order to clarify the mode of their action mainly in sclerotic hearts.

MATERIALS AND METHODS

The number of cases studied were as shown in Table I. Cardiac output and coronary blood flow were measured by the direct Fick method and by the nitrous oxide desaturation technic respectively. The myocardial metabolic studies were performed between the fifth to tenth minute of nitrous oxide desaturation period. After the completion of control studies, the following coronary vasodilators were administered and then the above mentioned procedures were repeated after the appropriate time.

The coronary vasodilators used, their dosage, the route of administration and the time interval between the use of medication and the second measurement were as follows; theophylline-ethylenediamine 250mg, 7-(γ -diisobutylamino- β -benzoyloxypropyl)-theophylline (TH 24) 250mg, 7-chlorethyltheophylline (ETE) 200mg, Persantin 10mg, Segontin 10mg, intravenously about 20 minutes; papaverine hydrochloride 1 mg per kilogram of body weight intravenously or intramuscularly about 20 minutes; nitroglycerine average 0.6 mg

ranging from 0.15 to 0.75 mg sublingually about 10 minutes, isosorbide dinitrate (Carvasin) 7.5–10.0 mg orally about 30 minutes, cytochrome C 40 mg intravenously about 30 minutes.

Coronary blood flow measurements were performed in 30 cases except for TH 24 and cytochrome C. In all 65 cases the myocardial gaseous metabolism and in almost all cases the myocardial glucose, lactate, pyruvate, citrate and non-esterified fatty acids (NEFA) metabolisms were studied. The analytical methods employed were described previously⁷⁾. The coronary-systemic flow ratio or resistance ratio were computed from coronary flow divided by cardiac output or from coronary resistance divided by systemic resistance in order to clarify the correlative changes between the coronary and systemic hemodynamics. The test was used for statistical analysis.

RESULTS AND COMMENTS

Systemic and Coronary Hemodynamics

Coronary blood flow. The coronary blood flow (ml/100 g/min)(Table II) was augmented by the administration of ETE, Persantin and Segontin, and the increase was 19%, 16% and 11% respectively. Following theophylline-ethylenediamine, it was noticeable that only a slight increase (4%) of coronary flow was observed in the coronary group, whereas it increased moderately (9%) in the congestive failure group, suggesting the coronary vasculature in the former more limited to dilate than in the latter. On the other hand, after nitrates and papaverine the coronary flow decreased 5% and 11% respectively. The results obtained after the use of nitrates coincided with

that of Gorlin and his co-workers¹⁾.

Coronary blood flow and arterial blood pressure. The mean arterial blood pressure was elevated by ETE, lowered by nitrates and Persantin significantly (Figure 1). It could be said from Figure 2 that ETE aug-

Fig. 1. Changes of mean arterial blood pressures after coronary vasodilators. The thick lines indicate the change of average values. T: theophylline-ethylenediamine, ETE: 7-chlorethyltheophylline, N: nitrates, P.H.: papaverine hydrochloride, P: Persantin, S: Segontin, Cyt. C: cytochrome C

Fig. 2. Correlative changes of coronary blood flow (CBF) and mean blood pressure after coronary vasodilators. The figure indicates the change of the average values. C.S.: coronary sclerosis, C.H.F.: congestive heart failure.

mented the coronary flow along with the blood pressure. Papaverine and nitrates reduced both parameters simultaneously, whereas the increase of coronary flow was brought about by Persantin and Segontin with only a slight change of blood pressure.

Coronary blood flow and cardiac output. Papaverine decreased the cardiac output significantly. ($p < 0.01$). Nitrates and Segontin

had similar tendencies. It could be said from Figure 4 that Persantin and Segontin raised coronary-systemic flow ratio moderately, papaverine slightly and nitrates a little, although theophylline-ethylenediamine and ETE had no influence on this ratio in the sclerotic hearts. Therefore, it seemed likely that the coronary vasodilators applied in this experiment increased the coronary flow relatively more than the cardiac output in varying degrees except for the theophylline derivatives.

Fig. 3. Changes of cardiac output after coronary vasodilators. The lower figure indicates average values.

Fig. 4. Average changes of coronary-systemic flow ratio, e.g. coronary flow divided by cardiac output. The figure expresses the postmedication values in % when the control ones would be 100%.

Coronary blood flow and left ventricular work (Figure 5). From the correlative changes of coronary flow and left ventricular work after the administration of coronary vasodilators, they could be divided into the following 3 groups; the first was Persantin and

Fig. 5. Correlative changes of coronary blood flow (CBF) and left ventricular work (L.V.W.) after coronary vasodilators.

Segontin with coronary flow increase against left ventricular work decrease, the second was papaverine and nitrates which decreased both parameters and the last was theophylline derivatives which augmented the coronary flow with or without little increase of left ventricular work.

Coronary and systemic resistance. The

systemic resistance was augmented by papaverine moderately ($p < 0.01$) and the same tendency was observed following Segontin and also in a much lesser degree after nitrates. On the other hand, the coronary resistance tended to decrease after Persantin and increased only slightly in papaverine. It had not shown any appreciable change following the use of other coronary vasodilators (Table 2). Thereupon the coronary-systemic resistance ratio decreased significantly after the administration of Persantin and papaverine and tended to lower following nitrates and Segontin (Figure 6). In other words, the coronary vasodilators except for the theophylline derivatives induced the relative reduction of coronary resistance as compared with the systemic one.

Myocardial Gaseous Metabolism

Myocardial oxygen consumption (MOC) and myocardial oxygen availability (MOA).

TABLE I NUMBER OF CASES, DIAGNOSIS AND ADMINISTERED CORONARY VASODILATORS

	Sclerotic Heart Disease				Congestive Heart Failure	Miscellaneous	Total
	Coronary Insufficiency	Angina Pectoris	Old Myocardial Infarction	Hypertension			
Theophylline-ethylenediamine	6	1	—	1	8	—	16
TH 24*	2	1	—	—	—	1	4
7-chlorethyltheophylline (ETE)	4	1	—	—	—	—	5
Nitrates	4	3	—	2	—	—	9
Papaverine hydrochloride	7	—	—	1	—	—	8
Persantin	2	5	3	—	—	—	10
Segontin	6	1	—	—	—	1	8
Cytochrome C	1	—	1	—	3	—	5
Total	32	12	4	4	11	2	65

* 7-(γ -diisobutylamino- β -benzoyloxypropyl)-theophylline

TABLE II AVERAGE CHANGES OF CORONARY BLOOD FLOW, CORONARY RESISTANCE AND SYSTEMIC RESISTANCE AFTER CORONARY VASODILATORS

Diagnosis	No. of cases	C.B.F. (ml/100 g/min)			Coronary resistance (mmHg/ml)			Systemic resistance (dyne sec. cm ⁻⁵)		
		before after change (%)			before after change (%)			before after change (%)		
Theophylline-ethylenediamine	Coronary Sclerosis	3	68.4	71.2	4.1					
	Congestive Heart Failure	3	74.2	81.2	9.4	1.27	1.17	-7.9	2165	2220 2.5
ETE	Coronary Sclerosis	4	66.1	78.6	18.9	1.55	1.50	-3.2	2773	2830 2.1
					($p < 0.02$)					
Nitrates	Coronary Sclerosis	5	89.1	85.0	-4.7	1.28	1.26	-1.6	1893	2003 5.8
Papaverine	Coronary Sclerosis	5	74.0	66.1	-10.7	1.90	2.07	8.9	2412	3185 32.0
								($p < 0.02$)		($p < 0.01$)
Persantin	Coronary Sclerosis	5	75.6	87.8	15.8	1.50	1.22	-18.7	2089	2135 2.2
Segontin	Coronary Sclerosis	5	87.9	97.3	10.7	1.06	1.02	-3.7	1529	1892 23.7

Fig. 6. Average changes of coronary-systemic resistance ratio, e.g. coronary resistance divided by systemic resistance. The figure expresses the postmedication values in % when the control ones would be 100%.

The changes of MOC and MOA (ml/100g/min) were dependent mainly upon that of coronary flow, so that both parameters inclined to decrease following the use of papaverine, nitrates and to increase by theophylline derivatives, Persantin and Segontin (Table III). It appeared likely that theophylline derivatives augmented more MOC than MOA in sclerotic hearts and, on the contrary, Persantin elevated MOA more than MOC. The percentage changes of both parameters following the others were nearly the same degree.

Myocardial oxygen extraction ratio. The ratio of MOC to MOA could be replaced with the ratio of coronary arterio-venous oxygen difference (ΔO_2) to arterial oxygen content, e.g. myocardial oxygen extraction ratio, since MOC or MOA are the product of coronary flow and coronary ΔO_2 or arterial oxygen content respectively. Thence the rise of oxygen extraction ratio indicates the in-

crease of MOC than MOA and the lowering of it indicates the augmentation of MOA than MOC, and thus the ratio shows directly the balance of oxygen demand and supply in the myocardium.

The changes of the oxygen extraction ratio after the coronary vasodilators applied in 65 cases, including TH 24 and cytochrome C were as follows: Theophylline-ethylenediamine, TH 24, ETE and papaverine elevated this ratio more or less. The change following theophylline-ethylenediamine was statistically significant. After the administration of Segontin and cytochrome C, the ratio did not show any change, whereas nitrates and Persantin lowered it significantly (Figure 7). It

Fig. 7. Changes of myocardial oxygen extraction ratio after coronary vasodilators. The lower figure indicates the change of average values.

was noticeable that the rise of this ratio by theophylline-ethylenediamine was larger in sclerotic hearts than in congestive hearts, suggesting that the coronary flow in the former was not easy to increase. Furthermore, it could be said that TH 24 and ETE seemed to be a little better than theophylline-ethy-

TABLE III AVERAGE CHANGE OF MYOCARDIAL OXYGEN CONSUMPTION (MOC) AND AVAILABILITY (MOA) AFTER CORONARY VASODILATORS

	MOC (ml/100 g/min.)			MOA (ml/100 g/min.)		
	Before	After	Change (%)	Before	After	Change (%)
Theophylline-ethylenediamine	6.5	7.9	+20.5 ($p < 0.05$)	10.6	11.3	+ 6.6
ETC	10.2	11.2	+10.1	12.0	13.4	+11.6
Nitrates	8.0	10.5	+31.3 ($p < 0.02$)	12.0	14.8	+23.3 ($p < 0.01$)
Papaverine hydrochloride	9.8	9.0	- 8.2	15.0	14.0	- 6.7
Persantin	8.7	7.9	- 9.2	13.0	11.6	-10.8
Segontin	9.0	10.1	+12.0	13.0	15.0	+15.6
	10.1	11.0	+ 8.9	14.7	16.0	+ 8.8

lenediamine in consideration of oxygen balance, since the elevation of the oxygen extraction ratio after the use of the former was in much lesser magnitude.

Myocardial mechanical efficiency. The reduction or the decreasing tendency of the myocardial mechanical efficiency was observed after the use of coronary vasodilators, especially the changes brought about by nitrates and papaverine were statistically significant.

Myocardial Carbohydrate and NEFA Metabolism

The myocardial glucose extraction ratio was elevated after cytochrome C administration ($p < 0.02$), and appeared to decrease by Persantin, but the others did not show any

Fig. 8. Changes of glucose extraction ratio ($\Delta G/Ga$, %) after coronary vasodilators. The lower figure indicates the average values.

specific effect on it (Figure 8).

The lactate extraction ratio quotient, which gives good measure of the disturbance of the myocardial lactate metabolism as previously described⁸⁾, was elevated by Persantin significantly ($p < 0.02$), and the increasing tendency was shown after the use of Segontin. On the contrary, it was lowered by theophylline-ethylenediamine ($p < 0.05$) and also seemed to fall following TH 24 and ETE (Figure 9).

The pyruvate extraction ratio quotient⁹⁾, the measure of myocardial pyruvate meta-

bolism, appeared to diminish after theophylline-ethylenediamine. The same tendency was induced by TH 24 and papaverine in a lesser degree (Figure 10).

Fig. 9. Changes of lactate extraction ratio quotient ($\Delta L/\Delta L_n$, %) after coronary vasodilators. The lower figure indicates the changes of the average values.

Fig. 10. Changes of pyruvate extraction ratio quotient ($\Delta P/\Delta P_n$, %) after coronary vasodilators. The lower figure indicates the changes of the average values.

As to the myocardial citrate metabolism, it seemed likely that papaverine and nitrates had alleviated the negative coronary arteriovenous difference, although theophylline derivatives had aggravated it slightly (Figure 11).

In observing the myocardial NEFA metabolism (Figure 12), it was shown that the coronary arteriovenous NEFA difference ($\Delta NEFA$) increased after theophylline derivatives, de-

Fig. 11. Correlative changes of arterial content (Ca) and coronary arteriovenous difference (ΔC) of citrate after coronary vasodilators. The figure indicates the changes of average values.

Fig. 12. Correlative changes of arterial content (NEFAa) and coronary arteriovenous difference ($\Delta NEFA$) of NEFA after coronary vasodilators. The figure indicates the changes of average values.

creased following cytochrome C, while the arterial NEFA level was elevated by them similarly. The $\Delta NEFA$ seemed to fall very slightly after the use of other coronary vasodilators.

Concerning the myocardial substrate usage (Figure 13, 14), Segontin had prone to increase the carbohydrate usage, although it decreased that of NEFA significantly ($p < 0.05$). Following papaverine, both parameters seemed to decrease, whereas ETE augmented only the NEFA usage significantly ($p < 0.01$). In the case of Persantin, the carbohydrate usage in all seemed to be unaltered as a consequence of the increased lactate and decreased glucose usage.

The carbohydrate and NEFA oxygen extraction ratio were computed by the formula employed by Bing¹⁰⁾, in order to com-

Fig. 13. Changes of myocardial glucose (upper figure) and lactate (lower figure) usage after coronary vasodilators. The thick lines indicate the changes of average values.

pare the changes of their contribution in the aerobic catabolism to the total myocardial oxygen extraction. The results were as follows (Figure 15): The carbohydrate oxidation in the myocardium seemed to be augmented by cytochrome C, although that of NEFA inclined to be depressed simultaneously. The similar metabolic changes were brought about in lesser magnitude by Segontin. On the other hand, the theophylline derivatives elevated the myocardial NEFA oxidation and tended to depress that of the carbohydrate. Furthermore, the NEFA oxidation had prone to be depressed slightly by papaverine.

The myocardial RQ as the overall sequela of the myocardial metabolism (Figure 16) elevated significantly toward the average

Fig. 14. Changes of myocardial NEFA usage after coronary vasodilators. The thick lines indicate the changes of average values.

Fig. 15. Average changes of substrate oxygen extraction ratio after coronary vasodilators. The figure expresses the post-medication values in % when the control ones would be 100%.

value of the normal controls after Persantin, Segontin and cytochrome C. Papaverine also had the same inclination, while nitrates appeared to lower the myocardial RQ. However, the myocardial RQ did not show any definite

Fig. 16. Changes of myocardial RQ after coronary vasodilators. The thick lines indicate the changes of average values.

change after theophylline derivatives. It could be said from the changes of myocardial RQ that the myocardial carbohydrate metabolism was augmented by Persantin, Segontin, cytochrome C and papaverine, while nitrates depressed it.

SUMMARY AND CONCLUSIONS

By the method of coronary sinus catheterization, the changes of myocardial metabolism after the administration of several coronary vasodilators were studied on 65 cases, mainly composed of coronary sclerotic heart diseases, in which the changes of coronary blood flow were investigated on 30 cases.

Though it remained to be justified as to the dosage administered and the time at which the second measurements were carried out, the mode of action of the applied coronary vasodilators appeared to be somewhat different from each other as follows.

1. The theophylline-ethylenediamine augmented the unbalance of the myocardial oxygen demand and supply, though it increased the coronary flow slightly. ETE increased the coronary flow moderately as well as the blood pressure. At this time it did not show any appreciable effect on the myocardial oxygen unbalance as same as TH 24. Theophylline derivatives as a whole had such a effect as to augment the lipid and to depress the carbohydrate metabolism of the myocardium.

2. Nitrates (nitroglycerin and Carvasin) did not increase the coronary blood flow, but lowered the blood pressure and cardiac output, resulting in the relative increase of coronary

blood flow and the relative reduction of coronary resistance in comparison with the systemic hemodynamics and as a consequence the improvement of myocardial oxygen balance was brought about. Furthermore, the myocardial carbohydrate metabolism seemed to be slightly depressed.

3. After the administration of papaverine hydrochloride, the relative increase of coronary flow and the relative decrease of coronary resistance were observed, since the reduction of cardiac output was significant in spite of decreasing tendency of coronary flow. However, this did not alleviate the myocardial oxygen unbalance. This also appeared to suppress the myocardial lipid metabolism.

4. Persantin brought about the augmentation of coronary blood flow accompanied with the reduction of coronary resistance resulting in the improvement of myocardial oxygen balance, while it lowered the blood pressure significantly without definite change of cardiac output. As to the metabolic effect, it was likely to depress the myocardial lipid metabolism slightly.

5. Following Segontin, the increase of coronary blood flow and the relative fall of coronary resistance were induced in spite of the reduction of cardiac output, without any appreciable improvement of myocardial oxygen balance. Metabolically it accelerated the myocardial carbohydrate combustion and coincidentally suppressed that of the lipid significantly.

6. Cytochrome C augmented the myocardial carbohydrate combustion with the likelihood of suppressing the lipid utilization, however the myocardial oxygen balance did not show any change.

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