

0310

✓
IX-7-11

**Glucose Blockage of the Increase in Stroke
Volume Produced by Smoking**

By **DAVID C. MOSES, B.A., DONALD POWERS, M.D.,
AND LOUIS A. SOLOFF, M.D.**

Circulation, Volume XXIX, June 1964

Glucose Blockage of the Increase in Stroke Volume Produced by Smoking

By DAVID C. MOSES, B.A., DONALD POWERS, M.D.,
AND LOUIS A. SOLOFF, M.D.

SMOKING (nicotine), in the postabsorptive state, increases the concentration of unesterified fatty acids (FFA) in the blood and also increases cardiac output. Soloff and Schwartz^{1,2} have presented evidence to indicate that peroral and intravenous glucose can block the fatty-acid response to smoking. This study shows that glucose can also inhibit the cardiac-output response to smoking by blocking the smoking-induced increase in stroke volume.

Material and Method

Seven healthy normal male paid volunteers (medical students and hospital employees) age 19 to 26 were studied. All were familiar with the type of tests to be performed. All were habitual smokers, smoking at least a pack of standard cigarettes a day. They refrained from eating at least 6 hours and from smoking at least 3 hours before the beginning of each experiment. Three different experiments were conducted on each subject on three different days so that each subject acted as his own control. The individual experiments were randomly performed. The subject rested supine in a thermostatically controlled room for at least ½ hour before the tests were begun. Each experiment was begun with a control recording of the cardiac output either in duplicate or in triplicate. The control outputs agreed within less than 10 per cent and averaged 7 per cent. On one day, the subject smoked two cigarettes within 10 to 15 minutes. When smoking of the second cigarette had been completed, the cardiac output was recorded and the time was called zero. Subsequent recordings were taken at 15, 30, 60, and 90 minutes. On another day, following the control record, 15 Gm. of a 10-per cent solution of glucose were administered intravenously within 5 to 10 minutes. The cardiac output was recorded immedi-

ately after the intravenous injection and 15, 30, 60, and 90 minutes thereafter. On still another day, a similar injection was given but this time it was followed by smoking two cigarettes within 10 to 15 minutes. The time of the recording of the cardiac output immediately after smoking was called 0 time, and recordings of the output were made 15, 30, 60, and 90 minutes thereafter.

The Stewart Hamilton dilution principle was used for determining the cardiac output. Because changes in cardiac output and not absolute figures were desired, the Shillingford Cambridge apparatus was used.

A vasodilating cream, Trafuril (Ciba), was applied to the pinna of the ear and a Cambridge earpiece cuvette was fastened to the ear and connected to a Cambridge dye-dilution recorder. Sufficient time was permitted to elapse to permit maximum dilatation of the vessels of the ear. A length of polyethylene tubing was inserted through a thin-walled 18-gauge needle into an antecubital, cephalic, or basilic vein and the distal tip was passed into the axillary vein or proximal to it. The other end of the tubing was connected to a three-way stopcock, which in turn was connected to the dye-dilution apparatus. Rapid injections of 40 mg. (2 ml. of a 2-per cent solution) of Coomassie-blue dye were made for each determination of the cardiac output. Rapid injections of the dye were facilitated either by flushing the dye through the catheter with 2 ml. of physiologic saline or by elevating the arm. Only clearly readable curves were accepted for measurement. The linear curves obtained were replotted on semilogarithmic paper, the descending limb was extrapolated to 0, and the curve was replotted linearly. The area under the curve was measured with a compensating planimeter. So long as the same amount of dye is used, the area under the curve is proportional to the cardiac output. This technic is also capable of determining, and has been used to determine, the actual cardiac output; but this was not necessary for the purpose of this study. The thought that smoking might cause vasoconstriction in the ear and result in inaccurate values for cardiac output was dispelled by Irving and Yamamoto's observation,³ that the arterial cuvette technic gave parallel findings and reflected the same changes, and by the nature

From the Department of Cardiology, Temple University Medical Center, Philadelphia, Pennsylvania.

Supported in part by the Tobacco Industry Research Committee, The Heart Association of Southeastern Pennsylvania, and The Arlene Dickler Research Fund.

Table 1

Hemodynamic Effects of Smoking and Glucose

Subject	Index*	Smoking					Smoking and glucose					Glucose							
		Control	0	15	30	60	90	Control	0	15	30	60	90	Control	0	15	30	60	90
S.H.	CO	100	110	94	109	145	100	105	100	84	107	97	100	66	74	72	94	140	
	SV	100	94	85	104	138	100	89	99	85	109	96	100	75	82	79	97	150	
	HR	100	117	111	105	105	100	118	102	99	102	102	100	88	91	91	97	94	
L.E.	CO	100	108	144	147	132	165	100	118	148	133	133	146	100	84	92	93	100	90
	SV	100	86	127	136	128	162	100	97	139	122	129	146	100	89	92	96	97	88
	HR	100	126	114	108	105	102	100	122	106	109	103	100	100	94	100	97	103	103
B.C.	CO	100	222	196	141	121	138	100	154	131	127	109	137	100	84	77	100	84	93
	SV	100	168	159	134	101	131	100	121	122	127	105	133	100	97	90	116	78	104
	HR	100	126	123	105	119	105	100	128	107	100	103	103	100	86	86	86	107	90
B.H.	CO	100	121	127	171	140	134	100	122	117	131	82	117	100	83	92	103	89	89
	SV	100	107	110	174	137	131	100	91	96	116	75	119	100	83	90	95	89	89
	HR	100	113	115	93	102	102	100	135	122	113	109	98	100	100	104	108	100	100
E.G.	CO	100	131	133	143	163	162	100	145	110	116	124	134	100	105	100	108	86	123
	SV	100	99	118	130	145	151	100	113	90	100	99	107	100	96	97	108	83	103
	HR	100	132	112	110	113	107	100	128	122	116	125	125	100	110	103	100	103	119
J.D.	CO	100	125	117	117	107	119	100	117	110	93	90	92	100	117	108	90	109	115
	SV	100	105	111	110	113	113	100	106	107	103	82	99	100	114	115	103	109	119
	HR	100	116	116	102	96	100	100	110	103	90	110	93	100	103	94	88	100	97
L.J.	CO	100	208	156	149	124	148	100	142	124	134	100	89	100	125	98	113	124	91
	SV	100	131	113	126	106	126	100	98	90	103	84	80	100	125	98	108	97	87
	HR	100	158	137	119	117	117	100	144	137	130	118	111	100	100	100	104	128	104
Avg.	CO	100	146	139	139	133	143	100	129	120	117	106	116	100	102	92	97	98	106
	SV	100	113	117	117	124	134	100	103	106	108	98	111	100	97	95	101	93	105
	HR	100	117	118	107	108	106	100	126	114	108	110	105	100	97	97	96	105	101

* Cardiac output (CO), stroke volume (SV), and heart rate (HR)—expressed as percentage of control.

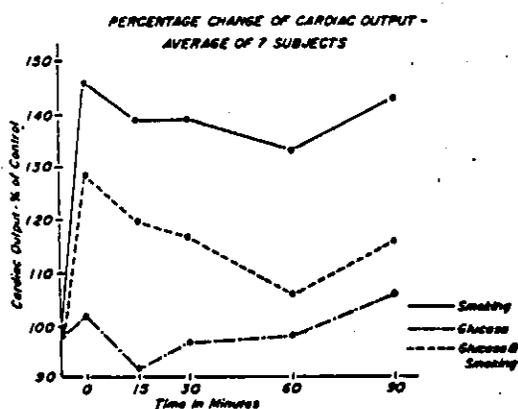


Figure 1

Average change in percentage of cardiac output after smoking, after glucose and smoking, and after glucose alone.

Circulation, Volume XXIX, June 1964

of this study. The vasodilating cream prevents vasoconstriction.

The average area for the cardiac output during the control period was given a value of 100 per cent. Subsequent determinations were expressed as a percentage of the control value. The heart rate was measured directly. The stroke volume for the control period (CO/HR) was also given a value of 100 per cent, and subsequent determinations were expressed as a percentage of the control value.

Results

Table 1 contains the detailed data on the hemodynamic effects of smoking and glucose.

Figure 1 shows that the cardiac output rises briskly after smoking and that this rise tends to persist for the duration of the experiment. These changes are statistically significant at the 1-per cent level at 0 time and at 15 minutes, at the 0.1-per cent level at 30 minutes, at

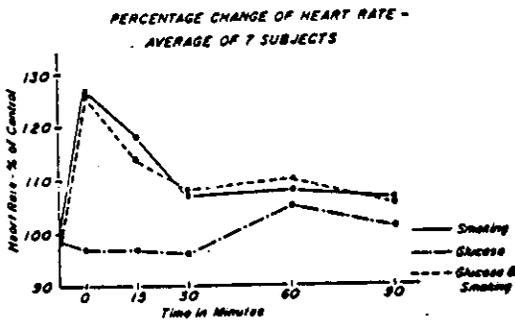


Figure 2

Average change in percentage of the heart rate after smoking, after glucose and smoking, and after glucose alone.

the 1-per cent level at 60 minutes, and at the 5-per cent level at 90 minutes.

Fifteen grams of glucose intravenously decreased the cardiac-output response to smoking. The initial brisk rise is lower, and even this rise is poorly sustained. The difference between smoking and smoking and glucose is not statistically significant at 0 time, and at 15 minutes is still slightly below statistical significance at the 5-per cent level, but at 30 minutes is significant at the 0.1-per cent level, at 60 minutes at the 1-per cent level, and at 90 minutes falls just below statistical significance at the 5-per cent level.

On the other hand, the cardiac-output response to smoking was statistically significantly different from that of glucose alone at all times and that of smoking preceded by glucose from that of glucose alone at 0, 15, and 30 minutes.

Figure 2 shows that the heart rate rises briskly at 0 time and falls rapidly within 30 minutes both after smoking and after smoking and glucose. There is no significant difference in heart rate whether smoking is or is not preceded by glucose.

On the other hand, smoking with or without preceding glucose produced a statistically significantly different heart rate from that of glucose alone at 0, 15, and 30 minutes.

Figure 3 shows that the stroke volume rises immediately after smoking and that this rise continues for the duration of the experiment. These changes are not statistically significant at 0 time, are significant at the 5-per cent level

at 15 minutes, at the 0.1-per cent level at 30 minutes, at the 1-per cent level at 60 minutes, and at the 5-per cent level at 90 minutes.

Fifteen grams of glucose intravenously decreases the stroke-volume response to smoking. These differences are not significant at 0 and 15 minutes, but are significant at the 0.1-per cent level at 30 minutes, at the 1-per cent level at 60 minutes, and just below the 5-per cent level at 90 minutes.

Although smoking produced significant changes in stroke volume compared to glucose at 15 minutes ($p < 0.05$), at 30 minutes ($p < 0.001$), and at 60 and 90 minutes ($p < 0.01$), the stroke volume after glucose and smoking was no different, at all times, from that of glucose alone.

Discussion

These observations that smoking increases cardiac output and stroke volume corroborate those of Irving and Yamamoto.³ They found similar results with cigarette and pipe smoking and when nicotine was given intravenously, but sham smoking produced no change.

The mechanism of these cardiac as well as the fatty-acid responses to smoking is easily understood on the basis of well-established effects of nicotine. The glucose inhibitory effect of the fatty-acid response to smoking is also explainable on the basis of the reciprocal relationship between glucose and fatty-acid metabolism. The mechanism of the glucose in-

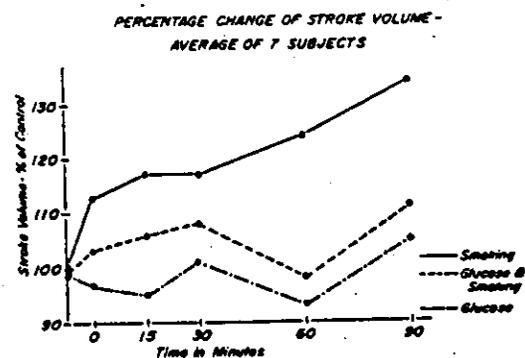


Figure 3

Average change in percentage of the stroke volume after smoking, after glucose and smoking, and after glucose alone.

Circulation, Volume XXIX, June 1964

hibitory effect on the cardiac output and of the stroke-volume response to smoking is not apparent.

Dole⁴ was the first to describe the drop in plasma FFA after glucose loading and suggested that a fall in blood sugar stimulates release of catecholamines, which in turn mobilizes FFA from fat deposits. He also demonstrated a rise in plasma FFA after the administration of epinephrine. White and Engel⁵ were the first to demonstrate that catecholamines could release FFA from adipose tissue in an albumin-containing medium and Gordon and Cherkas,^{6,7} in addition, showed that glucose and insulin in the medium reduce FFA release. The mechanism for this inhibition is through accelerating the uptake and re-esterification of FFA. An additional impedance to lipolysis was postulated by Carlson and Oro,⁸ and suggested by Hagen's work.^{9,10} Havel and Goldfien¹¹ have demonstrated an increase in plasma FFA in man and in dogs after an infusion of norepinephrine or epinephrine that returns shortly to normal after the infusion is stopped. Furthermore, this response is prevented by pretreatment with an adrenergic blocking agent.

Burn and Rand¹² have shown that nicotine can cause a release of catecholamines from extra-adrenal chromaffin cells found in cardiac and other tissues and norepinephrine from postganglionic sympathetic nerve endings. Watts¹³ has shown increased excretion of epinephrine after smoking in man and an increase in arterial blood epinephrine in dogs after intravenous nicotine but not after a ganglion blockage. Smoking, by releasing catecholamines, could mobilize FFA from fat deposits. If sufficient glucose is present in the blood to re-esterify FFA, however, an accelerated uptake and re-esterification of FFA (possibly with a partial inhibition of lipolysis) may prevent a rise in plasma FFA. The release of catecholamines mobilizes fatty acids but its appearance in the blood is blocked if sufficient glucose is present to re-esterify the fatty acids.

Such an explanation, however, does not account for the glucose-inhibiting effect on the

cardiac output and stroke-volume response to smoking.

Paoletti, Smith, Maickel, and Brodie¹⁴⁻¹⁶ have identified the presence of norepinephrine in adipose tissue of rats and rabbits. Moreover, they have presented evidence that norepinephrine in adipose tissue is essential in the mobilization of lipids induced by ACTH in vitro.

Edmonson and Goodman¹⁷ have been unable to confirm the essential role of adipose tissue in the release of FFA. They found that prolonged fasting releases FFA from adipose tissue from animals given huge doses of reserpine. Their findings point to the fundamental role of glucose in fat metabolism. Nonetheless, this evidence does not negate the concept of Paoletti et al. of the physiologic and significant role of norepinephrine in the release of FFA from adipose tissue. Their findings imply a parallelism between the concentration of triglycerides and of norepinephrine in adipose tissue. Glucose may therefore directly or indirectly be responsible for rebinding norepinephrine to adipose tissue during the time it is accelerating the uptake of and re-esterifying FFA. Such a process could decrease the amount of norepinephrine delivered to the heart. Such a mechanism could explain the block in stroke volume. The initial changes in heart rate could be due to a transient outpouring of epinephrine.

If such a mechanism actually exists, adipose tissue would not only be of value in supplying fuel to the body (heart and muscles) when needed, but would have a built-in mechanism for increasing cardiac stroke output to supply the tissues with this additional fuel.

In any event, these results indicate that the cardiac-output response to smoking cannot be characterized by studies limited to the post-absorptive state. After all, the amount of glucose used in these experiments is less than one fourth that present in the average American meal. The inhibiting effect of glucose on the responses to tobacco (cardiac output, stroke volume, and FFA) suggest that these may be nutritional responses rather than harmful ones.¹⁸ Our unpublished observations indicate that mild exercise after smoking produces

an additional rise in cardiac output and stroke volume. Reagan et al.¹⁹ could not demonstrate myocardial ischemia in coronary subjects even in the postabsorptive state.

Summary

The percentage changes in the cardiac output, stroke volume, and heart rate were determined in seven healthy habitual smokers after smoking, after glucose, and after smoking preceded by glucose. No significant changes occur after glucose. There is a significant increase in cardiac output, stroke volume, and heart rate after smoking. Pretreatment with glucose did not change the heart-rate response to smoking. Nevertheless, the cardiac-output response was diminished. This decrease is due to a block in the increase in stroke volume induced by smoking.

Acknowledgment

Herman Siple, M. S., Fels Research Institute, confirmed the statistical analyses.

References

1. SOLOFF, L. A., AND SCHWARTZ, H.: Plasma and red blood cell free fatty acid responses to glucose loading with a note on the effect of tobacco. *Am. J. M. Sc.* 246: 200, 1963.
2. SOLOFF, L. A., AND SCHWARTZ, H.: Interaction of glucose metabolism and smoking and its effect of PL-FFA. *Am. J. M. Sc.* 247: 5, 1964.
3. IRVING, D. W., AND YAMAMATO, T.: Cigarette smoking and cardiac output. *Brit. Heart J.* 25: 126, 1963.
4. DOLE, V. P.: A relation between the non-esterified fatty acids in plasma and the metabolism of glucose. *J. Clin. Invest.* 35: 150, 1956.
5. WHITE, J. E., AND ENGEL, F. L.: A lipolytic action of epinephrine and norepinephrine on rat adipose tissue *in vitro*. *Proc. Soc. Exper. Biol. & Med.* 99: 375, 1958.
6. GORDON, R. S., JR., AND CHERKES, A.: Unesterified fatty acid in human blood plasma. *J. Clin. Invest.* 35: 206, 1956.
7. SCHOTZ, M. C., AND PACE, I. H.: Effect of norepinephrine and epinephrine on nonesterified fatty acid concentration in plasma. *Proc. Soc. Exper. Biol. & Med.* 101: 624, 1959.
8. CARLSON, L. A., AND OHO, L.: Studies on the relationships between the concentration of plasma free fatty acids and glycerol *in vivo*. *Metabolism* 12: 132, 1963.
9. HAGEN, J. H.: The effect of hormones on glycerol levels in blood. *Fed. Proc.* 20: 204, 1961.
10. HAGEN, J. H., MOORHOUSE, J. A., AND STEENBERG, J.: Effect of insulin on plasma glycerine in man. *Metabolism* 12: 346, 1963.
11. HAVEL, R. J., AND GOLDFIEN, A.: The role of the sympathetic nervous system in the metabolism of free fatty acids. *J. Lipid Res.* 1: 102, 1959.
12. BURN, J. B., AND RAND, M. J.: The action of nicotine on the heart. *Brit. M. J.* 1: 137, 1958.
13. WATTS, D. T.: The effect of nicotine and smoking on the secretion of epinephrine. *In Cardiovascular effects of nicotine and smoking.* *Ann. New York Acad. Sc.* 90: 74, 1960.
14. PAOLETTI, R., SMITH, R. L., MAICKEL, R. P., AND BRODIE, B. B.: Identification and physiological role of norepinephrine in adipose tissue. *Biochem. Biophys. Res. Comm.* 5: 424, 1961.
15. SMITH, R. L., PAOLETTI, R., AND BRODIE, B. B.: The essential role of noradrenaline in corticotrophin-induced fatty acid mobilization. *Biochem. J.* 82: 51, 1961.
16. SMITH, R. L., PAOLETTI, R., AND BRODIE, B. B.: The identification and assay of noradrenaline in adipose tissue. *Biochem. J.* 82: 19, 1962.
17. EDMONSON, J. H., AND GOODMAN, H. M.: Effect of reserpine on fatty acid mobilization. *Proc. Soc. Exper. Biol. & Med.* 110: 761, 1962.
18. KERSHBAUM, A., BELLET, S., DICKSTEIN, E. R., AND FEINBERG, L. J.: Effect of cigarette smoking and nicotine on serum free fatty acids. *Circulation Research* 9: 631, 1961.
19. REAGAN, T. J., FRANK, M. J., MCGINTY, J. F., ZOBL, E., HELLEMS, H. K., AND BING, R. J.: Myocardial response to cigarette smoking in normal subjects and patients with coronary artery disease. *Circulation* 23: 365, 1961.