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 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 \( \frac{1}{2} \) 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 immediately 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-gage 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, that the arterial cuvette technic gave parallel findings and reflected the same changes, and by the nature.
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* 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.

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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
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. 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-

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**Figure 2**

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

**Figure 3**

Average change in percentage of the stroke volume after smoking, after glucose and smoking, and after glucose alone.
hibitory effect on the cardiac output and of the stroke-volume response to smoking is not apparent.

Dole \(^4\) 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 Engel \(^5\) were the first to demonstrate that catecholamines could release FFA from adipose tissue in an albumin-containing medium and Gordon and Cherkes,\(^6\),\(^7\) 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 Goldfien \(^11\) 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 Rand \(^12\) 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. Watts \(^13\) 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 Brodie \(^14\)-\(^16\) 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 Goodman \(^17\) 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 re-epinephrine. 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 re-binding 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.\textsuperscript{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**

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**References**


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