Cigarette smoking has been linked epidemiologically as a risk factor in the development of myocardial infarction and has been associated with an increase in sudden death among chronic cigarette consumers. The cause of this increased morbidity and mortality has not been established; among the factors under consideration are hypoxemia, enhanced coronary atherogenesis, increased platelet adhesiveness, and defective fibrinolysis.

Although it has long been known that cigarette smoking has acute effects upon the circulation, including increases in both heart rate and blood pressure, the implied cardiovascular stress produced in healthy subjects has not been assessed quantitatively nor its pathogenesis elucidated adequately.

Thus, the present study was designed to define non-invasively the hemodynamic effects of smoking a high-nicotine content tobacco cigarette vs an ultra-low nicotine content tobacco cigarette.

Materials and Methods

Study Design

Experiment 1

Comparison between a high-nicotine cigarette and a
nicotine-free synthetic smoking material cigarette. To determine if there were acute hemodynamic alterations attributable to smoking a tobacco cigarette, the following pilot study was performed. Thirteen healthy volunteers (six smokers and seven nonsmokers), eight women and five men ranging in age from 21-29 years, constituted the study population. Medical history, physical examination, chest roentgenogram and resting ECG were normal in all. None had eaten or smoked for at least 3 hours before being studied. After informed consent was obtained, baseline phonocardiographic, ECG lead II and carotid pulse tracings were recorded, and measurements of resting blood pressure by mercury sphygmomanometer were made with the subject in the supine position. Without change in posture, the subjects were asked to take one puff of a cigarette (lit and then held by a technician) at 15-20-second intervals, until 10 puffs had been inhaled. Within 2 minutes after termination of smoking, the phonocardiogram, the ECG and carotid pulse tracings were repeated.

The volunteers each participated in two sessions held on two days, during which they randomly smoked either a Kentucky reference cigarette (KRC)\(^9\) (2.5 mg nicotine) or a Cytrel synthetic smoking material cigarette (no nicotine). The type of cigarette used at each smoking session was known to the investigators but not to the volunteers.

Experiment 2

Comparison between a high-nicotine cigarette and a tobacco cigarette of ultra-low nicotine content. After experiment 1, comparing a high-nicotine tobacco cigarette and a nicotine-free synthetic smoking material cigarette, had demonstrated appreciable alterations in pulse, blood pressure and systolic time intervals after smoking the high-nicotine tobacco cigarette but not after the control cigarette, experiment 2 was performed to define echocardiographically the hemodynamic determinants of changes noted in systolic time intervals and to determine if such changes could be attributed solely to the nicotine content of the tobacco cigarette. The study population consisted of 16 normal human volunteers (10 men and six women), 12 chronic smokers, whose cigarette consumption ranged from 5-60 cigarettes per day, and four nonsmokers. They were 18-35 years old and had no cardiovascular disease as assessed by history, chest x-ray and physical examination. The resting ECG was within normal limits in all subjects. All volunteers did not eat or smoke for at least 3 hours before being

<table>
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<tr>
<th>Cigarette</th>
<th>Total particulate matter (mg/cigarette)</th>
<th>Nicotine (mg/cigarette)</th>
<th>Carbon monoxide (ppm/cigarette)</th>
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Abbreviation: ppm = parts per million.
cigarette to constant butt lengths were determined by standard techniques.  

**Analyses of Experimental Cigarettes**

The results of measurements on the reference cigarettes are presented in table 1. The synthetic smoking material pyrolyzed more rapidly, generating less carbon monoxide and less total particulate matter (which was devoid of nicotine) than the two tobacco products. Both tobacco cigarettes generated relatively high yields of total particulate matter and carbon monoxide.

**Recording Techniques**

Echocardiograms were recorded in all subjects with a Smith Kline Ekoline 20A Ultrascope and a 2.25-MHz, 1.27-cm transducer with a repetition rate of 1000 impulses/sec. The output signal was recorded on a Honeywell Visicorder Oscillograph, Model 1856. 

The echo probe was placed at the fourth intercostal space just to the left of the sternum and directed posteromedially to identify the mitral valve. The transducer was then rotated inferolaterally, and echoes from the endocardial surface of the left side of the interventricular septum and left ventricular posterior wall were visualized. Echo recordings of left ventricular dimensions were made only when supporting structures of the mitral valve apparatus or tips of the leaflets were observed simultaneously. Simultaneous tracings of lead II of the ECG and of a phonocardiogram using a contact microphone located and strapped about the third intercostal space left of the sternal border, as well as carotid pulse tracing with the transducer stabilized and strapped about the neck over a carotid artery were recorded. Both the phonocardiogram and the carotid pulse were recorded on a Cambridge multichannel physiological recorder in experiment 1, and on the Ekoline Ultrasonoscope in experiment 2. In the latter, they were recorded together with the echogram on the Honeywell Oscillograph at a paper speed of 5 cm/sec.

**Measurements and Calculations**

**Systolic Time Intervals**

The heart rate was determined by averaging five RR intervals on the ECG. Left ventricular ejection time (LVET) was measured by averaging the distance from the initial upward deflection of the carotid upstroke to the incisura of the same five consecutive cardiac cycles and corrected for heart rate according to Weissler's formula. The prejection period (PEP) was obtained by summing the distance from the Q wave of the QRS on the ECG to A2 on the phonocardiogram and then subtracting from that the uncorrected LVET of the same five consecutive cardiac cycles. The PEP was not corrected for heart rate. The ratio of PEP/LVET was formulated from uncorrected values. The triple product or time-tension index (TTI) was computed by multiplying systolic blood pressure by the LVET and the heart rate.

**Echocardiographically Derived Values**

Left ventricular dimensions were measured as follows: the end-diastolic dimension (Dd) was calculated at a point on the time-motion scan coincident with the peak of the R wave on the simultaneously recorded ECG. The end-systolic dimension (Ds) was defined as the smallest distance separating the left ventricular endocardial surfaces coinciding with a point immediately before A2 on the phonocardiogram. The ejection fraction (EF) was calculated by the cube method (Dd - Ds/Dd)3.13 The cardiac output was derived from the product of the heart rate and stroke volume (SV). Circumferential fiber shortening (Vcf) (circ/sec) was derived from the expression Dd - Ds/LVET × Dd. The posterior wall excursion (PWE) was measured, and the mean normalized velocity of posterior wall (VPW) was calculated from (PWE)/LVET × Dd. The carboxyhemoglobin levels were determined by a spectrophotometric method.

In measuring all parameters, the investigators were unaware of the cigarette used. All data were analyzed by paired t test.

**Results**

**Experiment 1**

**Comparison between high-nicotine tobacco cigarette (KRC) and nicotine-free synthetic smoking material cigarette.** Significant rises in pulse, systolic and diastolic blood pressure and corrected LVET and appreciable decrements in PEP and PEP/LVET were observed after smoking the nicotine reference cigarette, but not after smoking the nicotine- and tobacco-free synthetic cigarette. Smokers and nonsmokers behaved alike. The values before and after smoking of the high-nicotine cigarette were comparable to values derived in experiment 2.

**Experiment 2**

**Comparison between high-nicotine tobacco cigarette (KRC) and tobacco cigarette of ultra-low nicotine content (NFC) (table 2).** No significant differences in the parameters measured were noted after the sham smoking maneuver or between the resting states before smoking NFC and KRC (table 3).

After the subjects smoked one high-nicotine tobacco cigarette, the heart rate increased significantly from 64 ± 2 to 81 ± 4 beats/min (mean ± SEM), systolic blood pressure rose from 111 ± 2 to 122 ± 3 mm Hg, and diastolic blood pressure rose from 65 ± 1 to 74 ± 2 mm Hg. PEP decreased from 100 ± 3 to 85 ± 3 msec, corrected LVET rose from 403 ± 3 to 421 ± 6 msec and PEP/LVET declined from 0.329 ± 0.008 to 0.306 ± 0.010. Dd increased from 48.8 ± 1.1 to 51.6 ± 1.2 mm and Ds rose from 32.5 ± 1.1 to 33.4 ± 1.1 mm (figs. 1 and 2), EF increased from control of 70 ± 2% to 72.6 ± 2%, and the derived cardiac output rose from resting 5.3 ± 0.4 to 8.3 ± 0.8 1/min after smoking, paralleling an increase in SV from 83 ± 5 to 102 ± 7 ml after smoking KRC. Vcf increased from 1.12 ± 0.066 to 1.26
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± 0.096 circ/sec as VPW rose from 0.81 ± 0.03 to 0.88 ± 0.03 and TTI increased from 2110 ± 72 to 2850 ± 117 after subjects smoked KRC. Carboxyhemoglobin levels rose from control values of 2.7 ± 0.5 to 3.7 ± 0.6 vol% after KRC.

Table 2 also displays alterations in heart rate, systolic and diastolic blood pressure, systolic time intervals, left ventricular dimensions, normalized Vcf and mean normalized VPW before and after subjects smoked one tobacco cigarette of very low nicotine content (NFC). Mean heart rate rose from 64 ± 3 to 73 ± 4 beats/min. After smoking, as systolic blood pressure increased from 108 ± 2 to 113 ± 2 mm Hg and diastolic blood pressure rose from a resting level of 62 ± 2 to 68 ± 2 mm Hg, PEP fell from control 100 ± 3 to 93 ± 3 msec, while corrected LVET rose from 403 ± 8 to 420 ± 6 msec and PEP/LVET fell from 0.341 ± 0.009 to 0.319 ± 0.007. Dd remained unchanged but Ds diminished from 33.8 ± 1.0 to 32.1 ± 0.9 mm (figs. 1 and 2). SV increased from 91 ± 7 to 96 ± 7 ml, and EF increased from 69 ± 2% to 73 ± 2%. The derived cardiac output rose from 5.8 ± 0.6 to 6.8 ± 0.6 l/min. Vcf increased from 1.13 ± 0.06 to 1.21 ± 0.06 circ/sec and TTI increased from 2043 ± 78 to 2462 ± 84 after NFC. Carboxyhemoglobin levels rose from 2.5 ± 0.5 vol% at rest to 3.1 ± 0.5 vol% after smoking NFC.

Discussion

Smoking tobacco cigarettes of high- or low-nicotine content or nicotine-free cigarettes composed of synthetic smoking material increases the blood carboxyhemoglobin levels, which decreases the amount of oxygen available to the myocardium. However, smoking nicotine-free synthetic smoking material cigarettes has been shown to have no effect on blood pressure or heart rate, while smoking tobacco cigarettes with a high- or low-nicotine content has been shown to cause acute increases in heart rate and systolic and diastolic blood pressure, both in healthy subjects and in volunteers with coronary artery disease.16-19 These hemodynamic effects can be blunted or prevented by the administration of adrenergic blocking agents, so are presumably mediated either through an elevation in circulating catecholamines or an increase in norepinephrine elaborated from sympathetic axon terminals within tissues.20 The nicotine content of smoke is thought to be the cause of the catecholamine release that results in hemodynamic alterations.21

Direct changes in ventricular function induced by smoking have been less well documented. We have shown that smoking a nonnicotine, nontobacco cigarette does not alter systolic time interval measurements, and, recently, Jain et al.22 reported that the systolic time interval-derived ratio of PEP/LVET increased in chronic smokers with coronary artery disease but decreased in healthy volunteers after smoking two nicotine tobacco cigarettes, confirming our preliminary report.18 Studies by Aronow et al. in smokers with ischemic heart disease after consumption of several tobacco cigarettes showed a decrease in stroke index and EF documented by left ventriculography.23 They attributed this negative inotropic effect to rising levels of carboxyhemoglobin impairing oxygen delivery to an already compromised myocardium.

In the present study, the smoking of a high-nicotine tobacco cigarette by healthy subjects clearly resulted in an increase in heart rate, as well as a concomitant increase in afterload, reflected in a rise in systolic and diastolic blood pressures. PEP and PEP/LVET were decreased, and corrected LVET was prolonged. Echo-cardiography was used to clarify the cardiodynamic changes underlying the alteration in systolic time intervals. We observed increases in left ventricular Dd, calculated SV, EF, Vcf and VPW. The increase in SV explains the longer corrected LVET, and the increased EF, Vcf and VPW suggest enhanced contractility, accounting for the reduction of PEP and PEP/LVET. The end-systolic diameter also increased, presumably secondary to the increased afterload.

The first issue regarding the alterations in echocardiographically derived values, such as end-diastolic dimension and indices of contractility, i.e., EF, Vcf and VCW, is whether they represent direct effects of smoking on preload or are secondary to changes in heart rate and afterload. An increase in heart rate alone, however, has been associated with a decline in Dd and an increase in Vcf and VPW without altering EF and an elevation of blood pressure with an increment in Dd and an increase in Vcf and VPW, again without changing EF.24 Thus, the increments in Dd after smoking a high-nicotine cigarette genuinely reflect an increase in end-diastolic volume or preload, and an increase in Vcf, VPW and ejection fraction indicate heightened myocardial contractility. Additionally, atropine produced changes in heart rate and blood pressure in Hirschleifer’s study25 that were comparable to those observed after smoking a high-nicotine cigarette, but caused the end-diastolic dimension to decrease, while smoking resulted in an increase in the end-diastolic diameter.

The second issue is whether the observed changes in echocardiographic parameters reflect the hemodynamic response to an expansion of preload alone or whether they derive from an augmentation of preload coupled with a direct inotropic effect achieved by smoking a high-nicotine cigarette. In this regard, the smoking of a very low nicotine cigarette (NFC) sheds some light on the alteration in contractility, since SV notably rises after smoking an NFC, while end-diastolic volume or preload remains unchanged, indicating a direct, positive, inotropic effect of smoking a tobacco cigarette with virtually no nicotine. It appears, therefore, that the smoking of a high-nicotine cigarette causes an augmentation of preload coupled with a direct increase in inotropy, which show the effects of nicotine superimposed on the possible effects of other ingredients in the virtually nicotine-free cigarette.

The smoking of a tobacco cigarette of ultra-low nicotine content resulted in similar directional changes...
TABLE 2. Hemodynamic Parameters Before and After Smoking Kentucky Reference Cigarette and Nicotine-free Tobacco Cigarette

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<th>HR (beats/min)</th>
<th>Syst BP (mm Hg)</th>
<th>Diast BP (mm Hg)</th>
<th>PEP (msec)</th>
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Group data (Mean = ± SEM)

| B   | 2.7   | 64   | 111 | 65 | 100 | 0.329 | 48.8 | 32.5 |
| A   | 0.5   | 2    | 2   | ±1 | ±3  | ±0.008 | ±1.0 | ±1.1 |
| N   | 16    | 16   | 16  | 16 | 16  | 16    | 15   | 15   |

Abbreviations: A = after smoking; B = before smoking; COHb = carboxyhemoglobin; Dd = end-diastolic diameter; Diast BP = diastolic blood pressure; Ds = end-systolic diameter; HR = heart rate; LVET = left ventricular ejection time; NSm = nonsmoker; PEP = prejection period; Sm = smoker; Syst BP = systolic blood pressure; Vcf = mean normalized circumferential fiber shortening; VPW = mean normalized posterior wall velocity.

in heart rate and blood pressure. Significantly, echocardiographic values, e.g., EF, Vcf, SV, systolic time intervals and TTI, increased pari passu with measurements after inhaling the high-nicotine smoke. Although there was a significant rise in carboxyhemoglobin level after smoking the ultra-low nicotine cigarette, the magnitude of this rise was less than that noted after the smoking of the high-nicotine cigarette. The reason for this smaller, though significant, rise in carboxyhemoglobin level is not clear.

The significant changes in pulse, blood pressure, systolic time intervals and echocardiographic parameters after smoking the ultra-low nicotine cigarette implicate either minute amounts of nicotine or, more probably, other gaseous or particulate elements in tobacco cigarette smoke that operate directly or by means of catecholamine elaboration to cause positive inotropic effects. If nicotine alone were culpable, we would have expected a smaller change in the systolic time intervals or echocardiographic parameters with a cigarette containing a negligible amount of nicotine.
The positive inotropic effect of smoking an ultralow nicotine cigarette is emphasized particularly by
certaining that changes in pulse, blood pressure,
systolic time intervals and echocardiographic
parameters after smoking are not observed after
the smoking of a tobacco-free cigarette of synthetic
smoking material or after the sham smoking maneuver
(table 2). The latter control experiments also obviate
consideration of the effects of the rate or duration of
puffing, since these were uniform throughout the
study.

Our studies were carried out with the subjects in
the supine posture, and the alterations observed may not
be applicable to the upright position. Indeed, it has
been shown that venous return decreases in the upright
position after smoking a nicotine cigarette. Unfortunately, we have been unable to use single-plane
ecocardiography to visualize predictably both the in-
terventricular septum and posterior left ventricular
wall simultaneously in the upright subject to clarify
this finding.

To assess the immediate hemodynamic effects
non-invasively, recordings in this investigation were made
within 2 minutes after termination of smoking. Serial
tracings to ascertain when the return to baseline values
was achieved were not performed; hence, we gained no
knowledge of the duration of these effects. We in-
visted the effects of smoking only one cigarette,
TABLE 3. Circulatory, Systolic Time Interval and Echocardiographic Measurements Before and After Sham Smoking Maneuver in 10 Subjects

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>Blood pressure</th>
<th>PEP (msec)</th>
<th>PEP/LVET</th>
<th>LVETc (msec)</th>
<th>End-diastolic diameter (mm)</th>
<th>End-systolic diameter (mm)</th>
<th>EF (%)</th>
<th>Vef (circ/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>66 ± 3</td>
<td>110 ± 2</td>
<td>64 ± 2</td>
<td>100 ± 3</td>
<td>335 ± 10</td>
<td>409 ± 8</td>
<td>68 ± 3</td>
<td>1.12 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>65 ± 4</td>
<td>111 ± 2</td>
<td>64 ± 2</td>
<td>98 ± 2</td>
<td>328 ± 9</td>
<td>412 ± 7</td>
<td>69 ± 2</td>
<td>1.13 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
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</tr>
</tbody>
</table>

Values are mean ± SEM.

Abbreviations: HR = heart rate; PEP = preejection period; LVET = left ventricular ejection time; LVETc = left ventricular ejection time (corrected for heart rate); EF = ejection fraction; Vef = mean normalized circumferential fiber shortening.

which may accentuate the positive inotropic effects of nicotine or other ingredients and lessen the negative inotropic impact of carbon monoxide, since carboxyhemoglobin levels do not rise dramatically until several cigarettes have been smoked. Further, carbon monoxide may have less of a cardio depressant effect on healthy subjects with presumed normal coronary arteries than on patients with coronary disease, who may be affected more adversely by any decrease in oxygen delivery, as suggested by the findings of Jain et al., which indicate that after two nicotine cigarettes were smoked, contractility was augmented (PEP/LVET decreased) in normal volunteers but impaired (PEP/LVET increased) in coronary disease patients. Thus, studies are needed to assess changes in systolic time interval and echocardiographic mea-

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** A) The ECG, phonocardiogram, carotid pulse trace and echocardiogram taken before and after the subject smoked a high-nicotine tobacco cigarette (KRC). The end-diastolic and end-systolic diameters (Dd and Ds) both increase after KRC. B) Representative tracings taken before and after a very low nicotine tobacco cigarette (NFC). Dd remains unchanged and Ds decreases after NFC. PWE = posterior wall excursion; ET = ejection time.
measurements in normals after smoking several cigarettes of either high or negligible nicotine content and after inhalation of different levels of carbon monoxide.

Recently, Tachmes and associates compared the response of cardiac output, measured as pulmonary capillary blood flow by means of an acetylene rebreathing method, with the smoking of a high-nicotine (2.4 mg) tobacco cigarette vs a low-nicotine (0.1 mg) tobacco cigarette. They found that within 5 minutes after the high-nicotine cigarette was smoked, cardiac output reached a maximum increase of 32% over control, but increased only by 13% after a low-nicotine cigarette was smoked. The increases in cardiac output were effected primarily by increases in heart rate. For comparison, in the present study the increases in cardiac output in response to high- and low-nicotine cigarettes were 57 and 17%, respectively, at 2 minutes after cessation of smoking. Tachmes and associates attributed the increase in cardiac output observed after the low-nicotine cigarette to nicotine. In the light of the significant rise in cardiac output observed in the present study after smoking a very low nicotine cigarette (<0.02 mg), however, this interpretation must be challenged. Tachmes' observations are also compatible with our hypothesis of the presence of cardioactive substances other than nicotine.

In conclusion, by using systolic time interval measurements and echocardiography, we have shown that smoking a high-nicotine cigarette not only increases the heart rate and afterload, but also enhances other determinants of myocardial oxygen consumption, i.e., preload and contractility. Thus, it appears that smoking a nicotine cigarette induces the same physiologic responses as isometric exercise, i.e., increase in heart rate, afterload and preload, and, as isometric exercise is known to be in the postmyocardial infarction period, may be arrhythmogenic. Further, we have shown that an ultra-low nicotine content tobacco cigarette has similar impact on noninvasively derived values, implying that there may be other inotropic or chronotropic agents in tobacco cigarette smoke that are unknown.

Acknowledgments

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References

Assessment of Left Ventricular Ejection Fraction and Volumes by Real-time, Two-dimensional Echocardiography

A Comparison of Cineangiographic and Radionuclide Techniques

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SUMMARY Five different algorithms for determining left ventricular (LV) ejection fraction (EF) and volumes from two-dimensional echocardiographic examination (TDE) were compared with standard methods for obtaining EF and volume from x-ray cineangiography (cine) and EF from radionuclide ventriculography (RVG) in 35 patients. Although all methods correlated positively, the degree of correlation varied with the algorithm used. For EF determination, TDE algorithms (especially those using multiple planes of section) were superior to unidimensional algorithms commonly used with M-mode echocardiography. The best algorithm (modified Simpson’s rule) correlated well enough with cine EF ($r = 0.78$; see Table 1) and RVG EF ($r = 0.75$; see Table 2) to make clinically useful estimates. TDE volumes also correlated meaningfully with cine end-diastolic and end-systolic volumes ($r = 0.84$; $n = 70$) but were associated with a large standard error of the estimate (43 ml) and offered less advantage over unidimensional volume estimations. Quantitative application of TDE appears to be a useful noninvasive method of evaluating LVEF, but is not as useful for estimating LV volumes.

VENTRICULAR PERFORMANCE is one of the most important factors for the prognosis of acquired heart disease, whether treated medically or surgically.1-4 Measures of left ventricular performance such as chamber volume and ejection fraction (EF) are usually deemed most reliable when derived from cardiac catheterization data. Recently, several investigators have shown that EFs derived from radionuclide ventriculograms (RVG) correlate well with EFs derived from x-ray cineangiograms. Two-dimensional echocardiography (TDE) has been used qualitatively to identify regional abnormalities of left ventricular function,5-10 and there is preliminary data suggesting that it has promise in assessing global left ventricular performance.11-16 We compared EF and ventricular volumes obtained from TDE images with corresponding determinations derived from RVGs and from x-ray cineangiograms made at cardiac catheterization in the same series of patients. 

Methods

Patient Selection

Fifty patients scheduled for diagnostic cardiac catheterization underwent examination by TDE and RVG during the same hospitalization. Thirty-five of these patients were selected because they had studies of adequate quality for quantitative interpretation. Specific reasons for exclusion were technically inadequate echo (13 patients) and cineangiograms with excessive premature complexes (two patients). The clinical status of all patients was unchanged between studies. Twenty-six patients had coronary artery disease, four had valvular heart disease, four had com-
Acute hemodynamic effects of cigarette smoking in man assessed by systolic time intervals and echocardiography.
B D Rabinowitz, K Thorp, G L Huber and W H Abelmann

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