Are cardiovascular reflexes more commonly impaired in patients with bronchial carcinoma?

GA GOULD, MA SHWORTH, GTR LEWIS

From the Department of Respiratory Medicine, Ham Green Hospital and Bristol Royal Infirmary, Bristol

ABSTRACT Non-invasive tests of cardiovascular autonomic function were performed in 69 patients with histologically proved bronchial carcinoma and the results compared with those obtained in a group of age and sex matched controls. Only two patients were under 50 years of age, and with the exception of the heart rate response to deep breathing the tests performed have no accepted normal ranges in patients of this age. None of the patients had features of florid, disabling autonomic neuropathy. All the tests of autonomic function showed declining performance with age but in addition there were significant differences in the results when the two groups were compared. In the group with carcinoma the resting heart rate was higher ($p < 0.05$), the resting supine blood pressure lower ($p < 0.01$), and the postural fall in blood pressure greater ($p < 0.01$). Test results were not related to tumour histology, the presence of finger clubbing, drug history, or symptoms suggestive of autonomic dysfunction. Abnormal responses in tests of cardiovascular autonomic function are commonly found in elderly patients but bronchial carcinoma appears to have an additional effect. The precise mechanism of this effect remains a matter for speculation.

Bronchial carcinoma is associated with various forms of neuropathy and myopathy.\(^1\)\(^2\) Autonomic dysfunction has been reported both as a consequence of malignant infiltration of nerves\(^3\)\(^\sim\)\(^5\) and as a non-metastatic effect\(^6\)\(^\sim\)\(^13\), although the incidence of this syndrome is unknown. The most frequently reported symptoms of autonomic neuropathy are dizziness on standing and syncope, weakness, impotence, sweating abnormalities, and bowel or bladder disturbances.\(^14\)\(^\sim\)\(^15\) Diabetic patients with autonomic neuropathy are also more prone to sudden death, perhaps related to cardiac denervation.\(^16\) If autonomic dysfunction is a complication of bronchial carcinoma it may contribute to the non-specific frailty and malaise of these patients and might also account for some of the deaths that occur without an obvious cause.

In this study we have compared the results of cardiovascular autonomic function tests in a group of patients with proved bronchial carcinoma with the results in a group of age and sex matched controls to determine whether autonomic dysfunction is significantly more common in patients with bronchial carcinoma.

Patients and methods

From September 1982 to January 1983 inclusive all patients admitted for investigation of bronchial carcinoma were studied and the 69 with histologically proved tumours were included in the carcinoma group (54 men, 15 women; mean age 66 years). Sixty nine age and sex matched controls (54M, 15F; mean age 66 years) were studied concurrently; most of these patients were studied before elective non-thoracic surgery (for non-malignant conditions), and the rest of the group comprised non-acute medical and geriatric inpatients and those patients with negative results from investigations for bronchial carcinoma. Details of age, sex, regular medication, tumour histology, presence of finger clubbing, history of chronic bronchitis, and symptoms suggestive of autonomic dysfunction (postural dizziness, sweating abnormalities, or altered bowel function) were recorded (table 1). None of the patients studied was suffering from overt cardiac failure, chronic renal failure or diabetes mellitus and none gave a history of alcoholism.

The following tests of cardiovascular autonomic function were performed in sequence:
Are cardiovascular reflexes more commonly impaired in patients with bronchial carcinoma?

Table 1  Details of the two groups of patients

<table>
<thead>
<tr>
<th>Carcinoma</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No</td>
<td>69 (54M, 15F)</td>
</tr>
<tr>
<td>Age (y) mean</td>
<td>43–85</td>
</tr>
<tr>
<td>Tumour histology</td>
<td>38 squamous</td>
</tr>
<tr>
<td></td>
<td>9 anaplastic</td>
</tr>
<tr>
<td></td>
<td>9 oat cell</td>
</tr>
<tr>
<td>Finger clubbing</td>
<td>8</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>2</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>2 postural dizziness</td>
</tr>
<tr>
<td></td>
<td>2 diarrhoea</td>
</tr>
<tr>
<td>Medication*</td>
<td>1 postural dizziness and diarrhoea</td>
</tr>
<tr>
<td></td>
<td>1 diuretic</td>
</tr>
</tbody>
</table>

* Excluding benzodiazepines, non-opiate analgesics, and inhaled β2 sympathomimetics.

1 The heart rate and blood pressure were measured after the patients had rested supine for at least five minutes.
2 The heart rate response to deep breathing was measured with maximal breaths at a frequency of six breaths a minute, the mean values from three consecutive breaths being used and the results being expressed as the E:I ratio—that is, longest R-R interval during expiration shortest R-R interval during inspiration

3 The heart rate response to the Valsalva manoeuvre was measured during a strain of 40 mm Hg for 15 seconds, the results being expressed as the Valsalva ratio—that is, longest R-R interval during recovery shortest R-R interval during strain

4 The heart rate and blood pressure response to standing was measured, the maximum fall in blood pressure being recorded and the heart rate response being expressed as the 30:15 ratio—that is, longest R-R interval around 30th beat after standing shortest R-R interval around 15th beat after standing

R-R intervals were measured from an ECG. Blood pressure was measured to the nearest 5 mm Hg. All measurements and calculations were carried out inde-pendently by two investigators (GAG and MA) without knowledge of the patients’ details.

For statistical analysis of the results we used Student’s t test for group data.

Results

Details of the patients are shown in table 1. From analysis of individual patient’s results the presence of finger clubbing, history of chronic bronchitis, use of medication, and symptoms of autonomic dysfunction appeared to have little relationship to the results of the tests. One of the patients in the control group was taking a combined preparation of fluphenazine and nortriptyline but all of his test results were normal and he was therefore included in the analysis. None of the patients complaining of dizziness on standing had objective evidence of postural hypotension, and none of the eight patients with a postural fall in blood pressure of 30 mm Hg or more complained of faintness or syncope. Tumour histology also appeared to be unimportant, with no obvious correlation between tumour types and test results.

Although in the control group the 30:15 ratio, E:I ratio, and Valsalva ratio declined with increasing age, age had a greater effect in the group with carcinoma. In the latter these three tests showed the same effects.

Table 2  Results of autonomic function tests in carcinoma and control groups (mean (SD) with range)

<table>
<thead>
<tr>
<th>Test</th>
<th>Carcinoma</th>
<th>Controls</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>87 (20) 50–136</td>
<td>80 (13) 55–125</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Resting systolic blood pressure (mm Hg)</td>
<td>144 (24) 100–200</td>
<td>155 (23) 100–190</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>E:I ratio</td>
<td>1.19 (0.16) 1.0–1.75</td>
<td>1.21 (0.14) 1.03–1.65</td>
<td>NS</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.33 (0.28) 0.93–2.06</td>
<td>1.38 (0.27) 1.03–2.12</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure fall on standing (mm Hg)</td>
<td>13 (16) +30 to −70</td>
<td>6 (10) +15 to −30</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>30:15 ratio</td>
<td>1.02 (0.05) 0.91–1.18</td>
<td>1.03 (0.07) 0.92–1.24</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Student’s t test.
of age, but in addition a progressive increase in the
resting heart rate and the degree of postural fall in
blood pressure was observed with increasing age. In
both groups low values for the 30:15 ratio (1:0 or less)
were recorded so commonly as to make the test of
little diagnostic value.

The results of the tests for the two groups are
shown in table 2. In the group with carcinoma the
mean resting heart rate was higher, the systolic blood
pressure lower, and the postural fall in blood pressure
greater. There were smaller, non-significant
differences in the results of the other tests.

Discussion

Patients with bronchial carcinoma are often non-
specifically weak and frail for no obvious reason. If
impaired cardiovascular reflexes are a contributory
factor, intervention in the form of drug treatment or
fluid and electrolyte replacement to normalise these
reflexes may help to improve these patients' condi-
tion. Gross impairment of cardiovascular reflexes has
been reported in association with bronchial carci-

oma,8–13 with improvement in some cases8–12 after
treatment for the tumour. We did not observe
any cases of florid, disabling autonomic neuropathy
in our study, but since the natural history and preva-
ience of this syndrome is unknown we might have
been observing the early stages of autonomic dys-
function in some patients.

The tests performed in this study are standardised
and simple to perform at the bedside, and have sug-
gested normal ranges.15 17 18 The results reflect a gen-
eralised response to a complex series of reflexes that
depend not only on the autonomic nervous system
but also on the ability of the heart and blood vessels
to react appropriately. In young subjects we may
assume that abnormalities in the responses to these
tests nearly always represent autonomic damage; but in
the elderly, when multiple pathological conditions are
more likely, results must be interpreted with care
since normal ranges are more difficult to define19 20—absent or severely impaired cardiovascular reflexes may occur commonly, as is sug-
gested by our results for the response of the heart rate
response to standing (30:15 ratio). Some workers
have observed little effect of age on the 30:15 ratio18
or the Valsalva ratio,21 22 but very few subjects over
65 years were included in these studies. In studies that
have included geriatric patients other workers have
shown that the Valsalva ratio23 and the E:I ratio17
progressively decline with age and that large postural
falls in blood pressure are commonly found in the
elderly.24 25

Our results have confirmed the effect of age on car-
diovascular reflexes, but in addition we have observed
significant differences between the group with car-
cinoma and the control group. The other variables
recorded had no obvious relationship to abnormal
tests results; in the case of finger clubbing this was an
interesting observation since clubbing and hyper-
trophic osteoarthropathy may have some connection
with autonomic dysfunction, as the condition may be
reversed with vagotomy. Although previous workers
have suggested that non-metastatic complications of
bronchial carcinoma (neurological and biochemical)
are more common with oat cell tumours1 2 we found
no association with a tumour type. Our numbers are
probably too small to draw any conclusions about
this.

Our findings suggest that in patients with bronchial
carcinoma tests of cardiovascular function more com-
monly reveal impairment, but the cause of this is un-
certain. The most significant differences observed in
our carcinoma group (higher resting heart rate, lower
supine blood pressure, greater postural fall in blood
pressure) are non-specific markers of abnormal car-
diovascular function and, even though the more
specific tests of autonomic function (Valsalva ratio,
E:I ratio) also showed minor and non-significant
differences, the abnormalities may not indicate auto-
nomic neuropathy but may be due to other factors.
Disturbance of fluid and electrolyte balance is a likely
cause, as many of these patients will have a poor fluid
intake owing to anorexia and some will also be fe-
brile, both of which may cause dehydration. A few
patients will have inappropriate hormone secretion,
which will also affect fluid and electrolyte balance and
may disturb cardiovascular reflexes. Another factor
that may be important is coexisting abnormalities of
pulmonary function, since some patients will have
lung collapse or consolidation due to local tumour
effects, and many will have chronic airflow obstruc-
tion owing to their heavy smoking. The effects of ab-
normal pulmonary function on these cardiovascular
reflexes have not been studied in a large group of
patients, though one study showed impairment of the
Valsalva response in three patients with em-
physema,26 while another study found a normal Val-
salva response in 10 patients with chronic pulmonary
disease and no clinical evidence of right ventricular
failure.22 The severity of lung disease was not docu-
mented in either of these studies; in our patients a
history of chronic bronchitis had no obvious effect on
the results of the tests.

In summary, in a group of 69 elderly patients with
bronchial carcinoma and 69 age and sex matched
controls we have confirmed the finding that certain
cardiovascular reflexes decline with age, and showed
that some tests, such as the 30:15 ratio, may be of
little diagnostic value since low values occur very
commonly. We have also observed an effect of bron-
chial carcinoma, with significant differences in the mean values for the resting heart rate, supine blood pressure, and postural fall in blood pressure when the two groups are compared, although we encountered no patients with florid, disabling autonomic neuropathy of the sort previously reported. Other variables, such as tumour histology, regular medication, and symptoms suggestive of autonomic dysfunction, did not appear to influence test results. The cause of these observed differences is not apparent.

References

22. Levin AB. A simple test of cardiac function based upon the heart rate changes induced by the Valsalva manoeuvre. *Am J Cardiol* 1966;18:90–9.
Are cardiovascular reflexes more commonly impaired in patients with bronchial carcinoma?

G A Gould, M Ashworth and G T Lewis

Thorax 1986 41: 372-375
doi: 10.1136/thx.41.5.372

Updated information and services can be found at:
http://thorax.bmj.com/content/41/5/372

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/