

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

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**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.<sup>1,2</sup> Autonomic dysfunction has been reported both as a consequence of malignant infiltration of nerves<sup>3-5</sup> and as a non-metastatic effect,<sup>6-13</sup> 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.<sup>14,15</sup> Diabetic patients with autonomic neuropathy are also more prone to sudden death, perhaps related to cardiac denervation.<sup>16</sup> 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:

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Table 1 Details of the two groups of patients

	Carcinoma	Control
Total No	69 (54M, 15F)	69 (54M, 15F)
Age (y) range	43-85	46-87
mean	66	66
Tumour histology	38 squamous 11 adenocarcinoma 9 anaplastic 9 oat cell 1 alveolar cell 1 mesothelioma	
Finger clubbing	8	0
Chronic bronchitis	2	10
Autonomic symptoms	2 postural dizziness 2 diarrhoea 1 postural dizziness and diarrhoea	—
Medication*	2 digoxin and diuretic 2 diuretic 1 methyl dopa	4 diuretic 1 fluphenazine/nortriptyline (Motival)

\*Excluding benzodiazepines, non-opiate analgesics, and inhaled  $\beta_2$  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)

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

\*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' condition. Gross impairment of cardiovascular reflexes has been reported in association with bronchial carcinoma,<sup>6-13</sup> with improvement in some cases<sup>8,12</sup> 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 prevalence of this syndrome is unknown we might have been observing the early stages of autonomic dysfunction in some patients.

The tests performed in this study are standardised and simple to perform at the bedside, and have suggested normal ranges.<sup>15,17,18</sup> The results reflect a generalised 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 define<sup>19,20</sup>—absent or severely impaired cardiovascular reflexes may occur commonly, as is suggested 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 ratio<sup>18</sup> or the Valsalva ratio,<sup>21,22</sup> 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 ratio<sup>23</sup> and the E:I ratio<sup>17</sup> progressively decline with age and that large postural falls in blood pressure are commonly found in the elderly.<sup>24,25</sup>

Our results have confirmed the effect of age on cardiovascular reflexes, but in addition we have observed

significant differences between the group with carcinoma 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 hypertrophic osteoarthropathy may have some connection with autonomic dysfunction, as the condition may be reversed by vagotomy. Although previous workers have suggested that non-metastatic complications of bronchial carcinoma (neurological and biochemical) are more common with oat cell tumours<sup>1,2</sup> 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 commonly reveal impairment, but the cause of this is uncertain. 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 cardiovascular 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 autonomic 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 febrile, 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 obstruction owing to their heavy smoking. The effects of abnormal 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 emphysema,<sup>26</sup> while another study found a normal Valsalva response in 10 patients with chronic pulmonary disease and no clinical evidence of right ventricular failure.<sup>22</sup> The severity of lung disease was not documented 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.

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