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Partial pulmonary sympathetic denervation by thoracoscopic D2–D3 sympathicolysis for essential hyperhidrosis: effect on the pulmonary diffusion capacity

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In patients with essential hyperhidrosis (EH), a pathological condition characterized by increased activity of the upper dorsal sympathetic ganglia D_2–D_3, anatomical interruption at the D_2–D_3 level by thoracoscopic sympathicolysis (TS) is a safe and effective treatment. The D_2 and D_3 ganglia, however, are also in the pathway of sympathetic lung innervation, which may influence the pulmonary diffusion capacity for carbon monoxide (expressed as transfer factor for CO:*T*LCO, and as transfer coefficient for CO:*K*CO).

We therefore studied the effect of TS on *T*LCO and *K*CO in 50 EH patients: compared with pre-operative values, both *T*LCO ($-6{\cdot}7\%$, $P<0{\cdot}001$) and *K*CO ($-4{\cdot}2\%$, $P=0{\cdot}002$) were significantly decreased at 6 weeks after bilateral TS, an effect which was independent of the smoking status of the patients. In order to explain this phenomenon, the following pharmacological interventions were studied: (1) oral β_{1+2}-adrenoreceptor blockade with propranolol caused a comparable decrease of *T*LCO ($-6{\cdot}3\%$) and *K*CO ($-7{\cdot}5\%$) in matched normal subjects, but had no effect on *T*LCO and *K*CO in EH patients prior to TS; and (2) subsequent inhalation of the β_2-adrenoreceptor agonist salbutamol in a dosage suspected to cause alveolar β-receptor stimulation had no effect on *T*LCO and *K*CO, neither in the normal subjects, nor in EH patients (before and after TS).

Although the exact mechanism of the TS-induced decrease in *T*LCO and *K*CO remains speculative, these findings suggest that they may be related to a β_1-adrenoreceptor-mediated change in pulmonary capillary membrane permeability, although TS-induced changes in pulmonary blood flow or an interplay of both mechanisms cannot be excluded.

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Introduction

Thoracoscopic sympathicolysis (TS) at the level of the upper dorsal sympathetic chain ganglia D_2–D_3 is a safe and efficient treatment of essential hyperhidrosis (EH) refractory to conventional medical treatment (1,2). The D_2–D_3 ganglia are also in the pathway of the sympathetic innervation of the lungs and heart. Therefore, TS at the D_2–D_3 level may be expected to cause a (partial) sympathetic denervation of the central thoracic organs.

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Thoracoscopic sympathicolysis indeed influences cardiac autonomic function comparably with the effects of a (partial) β-receptor blockade; an asymptomatic but statistically significant decrease in heart rate at rest and at maximal exercise, as well as a decrease in diastolic blood pressure response to the handgrip test (3,4). Although the sympathetic innervation of the lungs is sparse, and probably of no functional importance in normal humans (25), TS does affect pulmonary function tests (PFT); we have observed an asymptomatic but significant decrease in forced expiratory volume in 1 s (FEV_1) (-3%) and total lung capacity (TLC) ($-2{\cdot}8\%$), and an increase in airway resistance (RAW) ($+30\%$) (5). After correction of these parameters for the small drop in lung volume [FEV_1/forced vital capacity (FVC), specific airway resistance (SRAW), specific airway

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conductance (SGAW), significant changes disappeared. The above-mentioned PFT changes could therefore be attributed to a small postoperative decrease in lung volume, probably secondary to the thoracoscopic procedure itself. The only other parameter that consistently and significantly decreased after TS, and disproportionately to the changes in lung volume, was forced expiratory flow after exhalation of 75% of the vital capacity (FEF_{75}) ($-7{\cdot}8\%$). It was therefore concluded that D_2–D_3 sympathetic denervation may be responsible for a decrease in maximal expiratory flow at low lung volumes, suggesting that, at least in EH patients, small airway bronchomotor tone is influenced by sympathetic innervation (5). Relatively little is known about the influence of the autonomic pulmonary innervation on the pulmonary diffusion capacity for carbon monoxide (*T*LCO and *K*CO). Autonomic factors may influence *T*LCO and *K*CO by alternating pulmonary blood flow and/or ventilation–perfusion relationships (alterations in airflow distribution) and/or pulmonary vascular permeability (6). In order to clarify the effects of the sympathetic innervation on the pulmonary diffusion capacity for carbon monoxide, *T*LCO and *K*CO were studied in 50 consecutive patients with EH, before and after TS.

In order to examine the mechanisms underlying the observed changes in *T*LCO and *K*CO after TS, further studies were performed on other EH patients and on normal subjects using autonomic modulation with an oral non-selective β-adrenoreceptor blocker (propranolol), and an inhaled β_2-adrenoreceptor agonist (salbutamol). Pharmacological β_{1+2}-adrenoreceptor blockade with propranolol was used to create a 'pharmacological sympathectomy', in the assumption that the functional sympathetic innervation of the lung – when actually present – is mediated via β-adrenoreceptors.

Inhaled salbutamol was used for two reasons. First, via its β_2-adrenoreceptor stimulation effects on airway smooth muscle receptors, the role of airway diameter changes in the changes in *T*LCO and *K*CO (7) could be studied. Second, salbutamol was inhaled via a spacer device (Volumatic®) and at a dosage of 400 μg; under these conditions, alveolar β-adrenoreceptor stimulation almost certainly occurs (8–11), enabling the study of the role of alveolar β-adrenoreceptor stimulation on the observed effects of TS and propranolol on *T*LCO and *K*CO.

Materials and Methods

SUBJECTS

Fifty consecutive patients with EH (15 men, 35 women, mean age $28{\cdot}4 \pm 8{\cdot}2$ years, range 13–52 years) underwent TS for the treatment of severe refractory EH (group A). A detailed medical history, with special emphasis on respiratory or cardiac disease, and a complete physical examination were performed 1–2 weeks before TS. Three patients had a history of atopic asthma (6%), but were currently free of symptoms and took no medication; 11 patients were smokers. All patients gave informed consent, and all tests were performed during routine preoperative screening. Three patients were lost for follow-up; results are therefore calculated on the remaining 47 patients.

In view of the observed effects of TS on *T*LCO and *K*CO in group A patients, other groups of EH patients and normal subjects were studied: 10 other consecutive non-smoking EH patients referred for TS [two men, eight women, mean age $27{\cdot}7 \pm 10{\cdot}2$ years, range 16–49 years (group B)]; nine other consecutive non-smoking EH patients referred for TS [five men, four women, mean age $28{\cdot}6 \pm 13{\cdot}1$ years, range 15–48 years (group C)]; and eight healthy non-smoking volunteers [two men and six women, mean age $29{\cdot}8 \pm 4{\cdot}6$ years, range 20–37 years]. The group B and group C patients and normal subjects took no medication, and had no history of cardiac or pulmonary disease.

All patients and normal subjects gave informed consent to the various study protocols, which were approved by the Medical Ethics Committee of the author's institution.

PULMONARY FUNCTION TESTS (PFT)

All smoking patients refrained from smoking for at least 12 h before PFT; therefore, carboxyhaemoglobin levels were not measured. The single breath pulmonary diffusion capacity for CO (transfer factor for CO or *T*LCO), and transfer coefficient for CO (*K*CO or $T\text{LCO}/\text{VA}_{\text{eff}}$, where VA_{eff} represents the effective alveolar volume) were measured in a SensorMedics 2200 PFT unit (SensorMedics BV, Bilthoven, the Netherlands). The gas mixture was composed of 0·3% carbon monoxide, 0·3% acetylene, 0·3% methane (CH4), 21% oxygen and a balance of nitrogen. It was inhaled after a maximal expiration and allowed to dilute and diffuse during breath holding at maximal inspiration. The gas concentrations and volume were continuously analysed during the entire post-breath-hold exhalation, enabling calculation of the mean gas concentrations over an appropriate expired volume interval (this method enables adjustment, when necessary, of discard and sample collection volumes after performance of the test). In all patients, the default discard volume of 750 ml was accepted. VA_{eff} was calculated from the corrected dilution of

CH_4 and the inspired volume (VI). Anatomical (150 ml) and instrumental (85 ml) dead space were subtracted from VI before VA_{eff} was calculated. The single breath estimate of residual volume (RV) was defined as VA_{eff} minus VI. VA_{eff} in litres BTPS was used to calculate *T*LCO, and *K*CO was calculated as *T*LCO/VA_{eff}. Breath-holding was preset to 10 s. Haemoglobin concentrations were previously measured in 10 other patients before and 6 weeks after TS; since no changes were observed, no systematic haemoglobin concentrations were determined. The subjects were studied at 50 m above sea level. Reference values were those of the ECSC (12). *T*LCO and *K*CO measurements were performed at the end of a complete PFT study, including spirometry and flow-volume loops on the same 2200 SensorMedics unit, and airway resistance, airway conductance and pulmonary volume measurements in a constant volume bodyplethysmograph (SensorMedics 6200 Autobox). The latter data have been analysed in a previous paper (6) and will not be used here, except for the TLC.

THORACOSCOPIC SYMPATHICOLYSIS

Bilateral TS was performed as previously described (2–4).

Study Design

STUDY OF THE EFFECTS OF TS ON *T*LCO AND *K*CO IN 47 EH PATIENTS (GROUP A)

Pulmonary function tests including measurement of *T*LCO and *K*CO (expressed in absolute values and in percent predicted) were performed 1 day before and 6 weeks after TS, in similar study conditions. In order to examine the possible role of smoking history on test results, PFT data were also separately analysed for smoking and non-smoking EH patients.

STUDY OF THE EFFECTS OF ORAL β-ADRENORECEPTOR BLOCKADE ON *T*LCO AND *K*CO IN GROUP B EH PATIENTS, AND IN NORMAL SUBJECTS. COMPARISON WITH THE EFFECTS OF SUBSEQUENT TS (GROUP B) AND OF SUBSEQUENT INHALED SALBUTAMOL (NORMAL SUBJECTS)

Baseline *T*LCO and *K*CO were determined in 10 group B patients 2 weeks before TS; thereafter 40 mg propranolol (Inderal®) was administered t.i.d. for 2 consecutive days, and on the morning of the third day. On the morning of the third day, PFT were repeated. Finally, 6 weeks after TS, PFT were again repeated. The effects of oral β-adrenoreceptor blockade and of TS on *T*LCO and *K*CO were compared.

Baseline *T*LCO and *K*CO were also determined in eight healthy subjects. Thereafter, propranolol (dosage and scheme, see above) was administered and PFT were repeated. In this group, inhaled salbutamol was then administered [400 μg via metered-dose inhaler (MDI) with spacer], and PFT were repeated 15 min later. In this group, the effects of oral propranolol and of subsequent inhaled salbutamol on *T*LCO and *K*CO were assessed.

STUDY OF THE EFFECTS OF SALBUTAMOL ON *T*LCO AND *K*CO IN GROUP C EH PATIENTS, BEFORE AND AFTER TS

Baseline PFT were performed 2 weeks before TS in group C patients, followed by inhalation of salbutamol (Ventolin®, 400 μg via MDI with spacer). Pulmonary function tests were repeated after 15 min. Similar tests were performed 6 weeks after TS.

STATISTICAL ANALYSIS

Data are expressed as mean values ± 1 standard deviation (SD). Comparison of baseline age, *T*LCO and *K*CO, and gender ratio between the various study groups and normal subject groups was performed using one way analysis of variance, and the Chi-square analysis of contingency table. The effects of TS on *T*LCO, *K*CO and TLC in group A patients were assessed with the paired *t*-test; differences in baseline PFT data between smokers and non-smokers were studied with the unpaired Student's *t*-test; and the changes in *T*LCO and *K*CO after TS in smokers *vs.* non-smokers were compared with the unpaired Student's *t*-test.

The effects of propranolol on *T*LCO and *K*CO within group B patients, and within normal subjects, were assessed with the Wilcoxon rank-sum test. The magnitude of changes in group B patients *vs.* normals was compared with the Mann–Whitney test. To compare the effects of TS with the effects of propranolol in EH group B patients, the Friedman test was used. The same test was used to compare the effects of salbutamol with the effects of propranolol in normal subjects. The effects of salbutamol on *T*LCO and *K*CO in group C EH patients before and after TS were assessed with the Wilcoxon rank-sum test. Significance was accepted at $P<0{\cdot}05$ (13).

TABLE 1. Patient characteristics and baseline *T*LCO and *K*CO data

	Group A	Group B	Group C	Normals
n	47	10	9	8
Age (years)	28·4 ± 8·2	27·7 ± 10·2	28·6 ± 13·1	29·8 ± 4·6
M:F	14/33	2/8	5/4	2/6
*T*LCO				
(mmol min^{-1} kPa)	10·18 ± 2·22	10·27 ± 1·98	10·78 ± 2·55	10·78 ± 3·44
(% pred)	103·4 ± 14·4	104·1 ± 10·2	103·8 ± 13·1	101·3 ± 16·2
*K*CO				
(mmol min^{-1} kPa^{-1} l^{-1})	1·83 ± 0·25	1·79 ± 0·2	1·83 ± 0·24	1·78 ± 0·23
(% pred)	85·8 ± 12·3	85·3 ± 10·2	85·7 ± 13	86·4 ± 11·5
TLC (l)	5·87 ± 0·98	5·67 ± 1·96	6·1 ± 0·98	6·74 ± 1·75
(% pred)	99·4 ± 15	102·3 ± 134	104·6 ± 16	106·6 ± 13
Alveolar volume (l)	5·76 ± 1·03	5·52 ± 1·04	5·9 ± 0·9	6·5 ± 1·92

Results are expressed as mean ± SD. There were no significant differences for the various parameters between groups (ANOVA), nor between TLC and VA within groups (*t*-test or Mann–Whitney test).
M:F, male:female ratio; *T*LCO, transfer factor for carbon monoxide; *K*CO, transfer coefficient for carbon monoxide; % pred, % predicted; TLC, total lung capacity.

Results

Baseline *T*LCO and *K*CO (in absolute values as well as in percent predicted) and patient characteristics similar in all study groups. Therefore, baseline diffusion capacity for CO can be considered normal in all EH patient groups (Table 1). Thoracoscopic sympathicolysis successfully relieved hyperhidrosis in all EH patients, thereby confirming the anatomical interruption at the D_2–D_3 level, and thus, the partial anatomical sympathetic denervation of the lungs. After TS, no patient experienced respiratory symptoms.

STUDY OF THE EFFECTS OF TS ON *T*LCO AND *K*CO IN 47 EH PATIENTS (GROUP A)

As compared with baseline values, *T*LCO (−6·65%, $P<0·001$) and *K*CO (−4·21%, $P=0·002$) had decreased slightly but significantly at 6 weeks after TS. Baseline *T*LCO was not significantly different in smokers (28·81 ± 5·2 ml min^{-1} mmHg^{-1}) as compared with non-smokers (30·59 ± 6·6 ml min^{-1} mmHg^{-1}, $P>0·05$), whereas baseline *K*CO was significantly lower in smokers (5·02 ± 0·79 *vs.* 5·57 ± 0·69 ml min^{-1} mmHg^{-1}, $P=0·03$). However, TS-induced changes in *T*LCO (−5·01 *vs.* −7·19%, $P>0·05$) and in *K*CO (−4·58 *vs.* −3·77%, $P>0·05$) were similar in smokers and non-smokers (Table 2).

STUDY OF THE EFFECTS OF ORAL β-ADRENORECEPTOR BLOCKADE ON *T*LCO AND *K*CO IN GROUP B EH PATIENTS, AND IN NORMAL SUBJECTS. COMPARISON WITH THE EFFECTS ON *T*LCO AND *K*CO OF SUBSEQUENT TS (GROUP B), AND OF SUBSEQUENT INHALED SALBUTAMOL (NORMAL SUBJECTS)

In EH patients, β-adrenoreceptor blockade by means of oral propranolol had no significant effects on *T*LCO and *K*CO. In the same patient group, however, *T*LCO (−8·2%) and *K*CO (−8·2%) had significantly decreased 6 weeks after TS. In normal control subjects, oral propranolol produced a significant decrease in *T*LCO (−6·3%) and in *K*CO (−7·5%), comparable to the effects of TS in EH patients, but in contrast with the effects of propranolol on *T*LCO and *K*CO in EH patients before TS. Subsequent inhalation of salbutamol in the normal subjects (who still were orally 'β-receptor blocked' by propranolol) had no effects on *T*LCO and *K*CO [Table 3(a, b)].

STUDY OF THE EFFECTS OF SALBUTAMOL ON *T*LCO AND *K*CO IN GROUP C EH PATIENTS BEFORE AND AFTER TS

Inhaled salbutamol had no influence on *T*LCO or *K*CO in EH patients, before or after TS. [After TS, baseline *T*LCO and *K*CO values, however, had decreased significantly as compared with

TABLE 2. Changes in *T*LCO, *K*CO and TLC in the EH patient group A and in smoking and non-smoking patients in group A

			Before TS		After TS		Percent change	Significance
*T*LCO	Total (n=47)		10·18 ± 2·22		9·5 ± 2·33		− 6·7	P<0·0001
(mmol min^{-1} kPa^{-1})	Smokers (n=11)		9·65 ± 1·74		9 ± 1·97		− 5	
	Non-smokers (n=36)	NS	10·25 ± 2·21	NS	9·61 ± 2·44	NS	− 7·2	
*K*CO	Total (n=47)		1·83 ± 0·25		1·75 ± 0·26		− 4·2	P=0·002
(mmol min^{-1} kPa^{-1} l^{-1})	Smokers (n=11)		1·68 ± 0·26		1·60 ± 0·26		− 4·6	
	Non-smokers (n=36)	P=0·03	1·87 ± 0·23	P=0·04	1·8 ± 0·26	NS	− 3·8	
TLC	Total (n=47)		5·98 ± 1·07		5·72 ± 0·95		− 2·9	P=0·003
(l)	Smokers (n=11)		6·17 ± 1		5·92 ± 1·1		− 4	
	Non-smokers (n=36)	NS	5·87 ± 0·98	NS	5·65 ± 0·97	NS	− 2·4	

Results are expressed as mean ± standard deviation. *T*LCO, transfer factor for carbon monoxide; *K*CO, transfer coefficient for carbon monoxide; TLC, total lung capacity; NS, not statistically significant; TX, thoracoscopic sympathicolysis; EH, essential hyperhidrosis.

TABLE 3(a). Effects on *T*LCO and *K*CO of oral propranolol and of subsequent TS in group B EH patients

$n=10$	Baseline		After propranolol		After TS
*T*LCO (mmol min^{-1} kPa^{-1})	$10{\cdot}27 \pm 1{\cdot}88$	NS	$9{\cdot}85 \pm 1{\cdot}97$	$P<0{\cdot}05$	$9{\cdot}34 \pm 1{\cdot}75$
*K*CO (mmol min^{-1} kPa^{-1} l^{-1})	$1{\cdot}79 \pm 0{\cdot}2$	NS	$1{\cdot}73 \pm 0{\cdot}2$	$P<0{\cdot}05$	$1{\cdot}64 \pm 0{\cdot}25$

See Table 2 for legend.

TABLE 3(b). Effects on *T*LCO and *K*CO of oral propranolol and of subsequent inhaled salbutamol in normal subjects

$n=8$	Baseline	After propranolol	After salbutamol
*T*LCO (mmol min^{-1} kPa^{-1})	$10{\cdot}78 \pm 3{\cdot}44$	$10{\cdot}0 \pm 3{\cdot}42$	$10{\cdot}23 \pm 3{\cdot}37$
		$P<0{\cdot}05$	NS
*K*CO (mmol min^{-1} kPa^{-1} l^{-1})	$1{\cdot}78 \pm 0{\cdot}23$	$1{\cdot}64 \pm 0{\cdot}12$	$1{\cdot}63 \pm 0{\cdot}16$
		$P<0{\cdot}05$	NS

See Table 2 for legend.

TABLE 4. Effects on *T*LCO and *K*CO of inhaled salbutamol in group C EH patients before and after TS

	Before TS		After TS	
$n=9$	Baseline	Salbutamol	Baseline	Salbutamol
*T*LCO (mmol min^{-1} kPa^{-1})	$10{\cdot}78 \pm 2{\cdot}55$	$10{\cdot}79 \pm 2{\cdot}44$	$9{\cdot}62 \pm 2{\cdot}99$*	$9{\cdot}95 \pm 2{\cdot}37$
	NS		NS	
*K*CO (mmol min^{-1} kPa^{-1} l^{-1})	$1{\cdot}83 \pm 0{\cdot}24$	$1{\cdot}83 \pm 0{\cdot}26$	$1{\cdot}72 \pm 0{\cdot}26$*	$1{\cdot}76 \pm 0{\cdot}21$
	NS		NS	

See Table 2 for legend.
*As compared with baseline before TS.

pre-operative values, confirming the findings in the study of EH patients (group A) (Table 4)].

Discussion

This study shows that partial sympathetic denervation of the lungs by means of bilateral thoracoscopic D_2–D_3 sympathicolysis in patients with EH produces an asymptomatic, but statistically significant decrease in the CO diffusion capacity of the lung, expressed as *T*LCO and *K*CO. This decrease cannot be attributed to the small decrease in TLC which is observed after thoracoscopy (5) because the decrease in *T*LCO ($-6{\cdot}7\%$) is disproportionate to the decrease in TLC ($-2{\cdot}8\%$), and persists after correction for lung volume (*K*CO $-4{\cdot}2\%$ change). Furthermore, although an inverse relationship between alveolar volume and *K*CO has been observed (14–16), this is most pronounced at volumes below 80% of TLC. Above this volume, the relationship is constant (14,17). The small but significant drop in *T*LCO and *K*CO after TS, observed in EH patients, therefore represents a real change.

Is this change due to the act of thoracoscopy in itself, or to the sympathetic denervation of the lung? To the authors' knowledge, there are no data on PFT

changes (including *T*LCO and *K*CO) after thoracoscopy in patients without lung or pleural diseases. However, it seems very unlikely that a minimally invasive technique such as thoracoscopy, without any intervention on the lung, would permanently influence the pulmonary diffusion capacity. Furthermore, PFTs were obtained 6 weeks after thoracoscopy, a period which was long enough for complete recovery from anaesthesia and the sequellae of thoracoscopy (chest pain). It is therefore hypothesized that the observed changes in *T*LCO and *K*CO are attributable to the partial pulmonary sympathetic denervation, rather than to the thoracoscopic intervention.

The pulmonary diffusion capacity can be influenced by various factors (6,17), which may be related to: (1) changes in the diffusion characteristics of the alveolocapillary membrane (Dm); and (2) changes in the diffusion characteristics of the red blood cells in the capillary bed (Q·Vc), according to the model of Roughton and Forster (18) describing gas transport between the alveolar space and the red blood cells by the equation:

$$1/DL = 1/DM + 1/Q \cdot Vc$$

where DL is the diffusion capacity of the whole lung.

Within-subject changes in Dm can occur because of changes in alveolar surface (alveolar volume) or changes in alveolocapillary membrane thickness. The observed change in TLC, and therefore alveolar volume [in healthy lungs, alveolar volume is similar to TLC (19)], however, cannot explain the changes in *T*LCO and *K*CO (see above). Structural changes in the diffusion membrane, as can be seen, e.g. in interstitial lung diseases, are highly unlikely to occur after TS. Thickness and composition of the diffusion membrane could, however, theoretically be changed after TS, e.g. by an increase in interstitial fluid content due to increased vascular permeability; the latter may be influenced by β-adrenoreceptor activity in the alveolar wall. Indeed, autoradiographic labelling studies have revealed a dense labelling of β-adrenoreceptors in the alveolar walls accounting for more than 90% of total β-receptors in human lung. Approximately 30% of these receptors are of the β_1-subtype, and 70% of the β_2-subtype (20). The function of these abundantly present alveolar β-adrenoreceptors is unclear but may be involved in the regulation of capillary permeability (20), e.g. in the rat, β-receptor stimulation causes a decrease in capillary permeability (21). Furthermore, the presence of as many β_1-receptors is surprising since no sympathetic innervation of the alveolar walls has been demonstrated (22), which defies the idea that all β_1-adrenoreceptors are 'innervated' (20).

The TS-induced decrease in *T*LCO and *K*CO hypothetically may be explained by a TS-induced decrease of β-receptor activity in the lung, thereby increasing pulmonary vascular leakiness and interstitial fluid content. Since we have previously shown (30) that TS is followed by a significant decrease in plasma norepinephrine (β_1-receptor mediator) whereas plasma epinephrine (β_2-receptor mediator) remains unchanged, the TS-induced effect on alveolocapillary permeability is probably mediated via a decrease in β_1-receptor activity.

This mechanism is compatible with the observed decrease in *T*LCO and in *K*CO in normal controls after β-receptor blockade by means of propranolol, which is comparable to the decrease in *T*LCO and *K*CO after TS in EH patients. However, in the presence of an intact sympathetic innervation (prior to TS), oral propranolol had no effects on *T*LCO and *K*CO in EH patients. This may be explained by non-adrenergic effects of sympathetic pulmonary innervation or by a competition effect; the hypersympathicotony in EH (3,4) may have 'protected' against propranolol. In EH patients, higher doses of propranolol are perhaps needed to achieve complete β-receptor blockade, although heart rate had decreased significantly in the EH patients and in the normal patients. The observation that inhaled salbutamol, a specific β_2-adrenoreceptor agonist, has no effect on *T*LCO and *K*CO in EH patients (before or after TS) supports our hypothesis that the TS-associated decrease in *T*LCO and *K*CO is mediated through a β_1- and not a β_2-adrenoreceptor related mechanism. However, another explanation for the lack of effect of inhaled salbutamol may be that its dosage may have been too small to counteract the β-receptor blocking action of propranolol. Further studies using higher inhaled dosages, or intravenous administration, are necessary to confirm or refute this hypothesis.

The Q·Vc factor basically consists of pulmonary capillary blood volume, blood haemoglobin concentration and CO back pressure (6,17). Changes in pulmonary blood flow (independently of possibly associated changes in vascular permeability, see above) can indeed alter the pulmonary diffusion capacity (6). However, with respect to the *T*LCO as a measure related to the size of the capillary bed, it is of interest that a doubling of pulmonary blood flow does not appreciably alter *T*LCO (23,24). Nevertheless, *T*LCO increases in parallel with an increase in pulmonary capillary blood flow provided that mean pulmonary artery pressure (PPA) is also allowed to increase (25). Parallel to changes in PPA or pulmonary vascular resistance, infusion of atropine causes a decrease in *T*LCO, and norepinephrine and iso-

proterenol infusion induce an increase in T_{LCO} of about 10–20% (26). In dogs, α- and β-adrenoreceptor blockade resulted in pulmonary vasodilation and vasoconstriction, respectively, whereas cholinergic blockade causes pulmonary vasodilation at higher levels of blood flow (27).

According to these data, and irrespective of changes in vascular permeability, TS-associated decreases in T_{LCO} and K_{CO} may therefore also be mediated through TS-induced changes in pulmonary artery pressure and/or pulmonary blood flow. Although plausible, this mechanism would seem quantitatively less important than the 'vascular permeability hypothesis', because there are much less β-adrenoreceptors present at the smooth muscle of vessels, and because they are entirely of the β_2-receptor subtype (20). Since TS is associated with a decrease in norepinephrine ('β_1-mediator') and not in epinephrine ('β_2-mediator') (30), and because an inhaled β_2-adrenoreceptor agonist (salbutamol) in a dose sufficient for 'systemic' effects had no effect on T_{LCO} and K_{CO}, this mechanism is less probable, although it cannot be excluded.

A decrease in blood haemoglobin concentration after TS could also explain the observed decrease in T_{LCO} and K_{CO} (6). However, TS is a completely bloodless intervention, and blood haemoglobin concentrations in 10 EH patients before and 6 weeks after TS were similar ($14{\cdot}8 \pm 1{\cdot}3$ *vs.* $14{\cdot}7 \pm 1{\cdot}4$ g dl^{-1}, $P>0{\cdot}05$).

The serial measurements of T_{LCO} and K_{CO} in the pharmacological tests theoretically also could have been influenced by an increase in back pressure of capillary carbon monoxide, thereby reducing the available binding sites at the haemoglobin molecule (28). However, up to nine serial measurements of T_{LCO} and K_{CO} with 10-min intervals in five healthy volunteers did not cause significant changes in T_{LCO} and K_{CO} (data not shown).

Finally, the pulmonary diffusion capacity may be influenced by associated changes in (expiratory) flow rates (7). Airflow obstruction indeed has been shown to overestimate the single breath carbon monoxide diffusion capacity (29). However, since TS was shown to induce a decrease in FEV_1 and in FEF_{75} (5), T_{LCO} and K_{CO} would be expected to increase after TS. Furthermore, inhaled salbutamol, an agent predominantly acting on airway diameter and thus flow rates, did not influence the T_{LCO} or K_{CO}.

In conclusion, upper dorsal thoracoscopic sympathicolysis performed for the treatment of EH, causes an asymptomatic but statistically significant decrease in T_{LCO} and K_{CO}, the exact mechanism of which remains unclear. Pharmacological modulation studies suggest that β_1-adrenoceptor-mediated changes in pulmonary capillary membrane permeability may be responsible, although changes in pulmonary blood flow and/or pressure also may be involved.

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