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Early symptom-relief after valvulotomy in mitral stenosis indicates role of lobeline-sensitive intrapulmonary receptors

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ABSTRACT

Respiratory sensations of eight patients with mitral stenosis in response to i.v. lobeline and 6-min walk before percutaneous mitral valvulotomy (PMV) were 'being short of breath', pressure in chest, tracheobronchial irritation, a desire to cough, persistent dry cough, chest pain and were qualitatively similar amongst 75% ($P = 0.005$) of the patients. A week after PMV lobeline evoked similar sensations but the threshold dose decreased from 32.4 ± 3.8 to 24.1 ± 3.2 μg/kg ($P = 0.001$) and pulmonary artery wedge pressure (PAwP), signifying reduction in pulmonary congestion, from 23.1 ± 1.4 to 14.3 ± 3.4 mmHg ($P < 0.001$). Distance walked in 6 min increased from 217 ± 58 to 319 ± 51.6 m; and mitral valve area from 0.63 ± 0.01 to 1.43 ± 0.26 cm^2 ($P < 0.001$).

A fall in lobeline-sensation threshold dose indicated reduction in pulmonary congestion and stimulus to juxtapulmonary/J (or pulmonary C fibre) receptors which suggests that they had contributed to the respiratory and viscerosomatic symptoms seen before PMV.

1. Introduction

The principal clinical manifestation of mitral stenosis (MS), a condition that is characterized by a raised left atrial pressure due to an obstructed mitral valve orifice, is dyspnoea. Additionally in some patients, routine physical tasks and short distance walking gives rise to chest pain or dry cough (Braunwald, 1988). These symptoms correlate well with raised intracardiac pressures, since once the head of pressure that forces blood into the left ventricle is reduced, as with percutaneous mitral valvulotomy (PMV) there is an immediate amelioration of respiratory symptoms and resumption of increased physical activity with excellent prognosis (Tuzcu et al., 1992; Stefandis et al., 1992; Marzo et al., 1993). The underlying mechanisms that have been proposed for the genesis of these symptoms are pulmonary venous congestion leading to worsening of all aspects of lung function, partly attributable to a reduced vital capacity (Tanabe et al., 1993), hypo perfusion of skeletal muscle resulting in biochemical and other anatomical changes, which account for limitation in physical activity (Mancini et al., 1989). However, dyspnoea-free increase in physical activity and exercise seen as early as 2–6 days after valvulotomy, a period marked by the disappearance of pulmonary congestion, but when neither skeletal muscle peak exercise oxygen consumption (Marzo et al., 1993) nor muscle structure or biochemistry change (Barlow et al., 1995), and lung-function abnormalities still persist (Gomez-Hospital et al., 2005), indicate that factors other than these contribute to the early relief that is seen.

Reed et al.'s study (1978) engendered the possibility that dyspnoea seen in these patients arises not only from a reduced vital capacity of the lungs due to pulmonary congestion, but also reflexely via stimulation of intrapulmonary sensory receptors, e.g. the juxtapulmonary capillary or J receptors—a conclusion they based on the stimulation of these receptors in animals, by pulmonary congestion and by intravenously injected chemicals to give rise reflexely to tachypnoea (Paintal, 1955, 1969; Coleridge and Coleridge, 1978). 80% of these receptors as discussed earlier (Dehghani et al., 2004) are innervated by vagal 'C' or unmyleinated fibres and 20% by 'A-delta' or myelinated fibres and are also referred to as pulmonary C fibres.

An earlier study in mitral stenosis patients and normal subjects by Stern et al. (1966) showed that 3 mg/ml lobeline, an alkaloid, injected into different locations in and around the cardiac chambers produced a cough but not when injected into the left ventricle or into a distal branch of the pulmonary artery. This led them to conclude that these respiratory reflexes arose from sensory receptors accessible to lobeline through pulmonary and not systemic circulation. This, therefore, excludes the origin of lobeline-induced

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sensations and reflexes from sensory receptors accessible through the bronchial circulation, e.g. bronchial C fibre receptors (Anand, 2000), or the systemic circulation, e.g. slowly (SARs) and rapidly adapting pulmonary stretch receptors (RARs) located in the carina, trachea and bronchi and also the central ones described by Dwoskin and Crooks (2002).

A later correlative study of animals and human subjects demonstrated that smaller doses of lobeline i.v. (10–15 μg/kg) gave rise to distinct sensations in the upper respiratory areas accompanied by respiratory reflexes and larger doses (30 μg/kg) to a dry cough reflexely, by stimulation of J (pulmonary C fibre) receptors (Raj et al., 1995). It also showed that the presumed increase in activity of the rapidly adapting pulmonary stretch receptors (RARs) in humans, a small percentage of which is accessible through pulmonary circulation, with forced expiration to residual volume at the time the lobeline-induced sensations were expected, did not enhance the sensation in any subject and obviated their role in these sensations. Furthermore, the dry cough produced by lobeline i.v. was demonstrated to be a reflex and not a behavioural response (Raj et al., 2005).

The present study was undertaken to determine if J (pulmonary C fibre) receptors which are accessible through the pulmonary circulation and which would have been stimulated by the underlying pulmonary congestion in mitral stenosis patients, give rise to their reflex effects or not. This was carried out in MS patients by scrutinizing the nature of respiratory sensations or symptoms evoked by a 6-min walk test and those arising from an intravenous delivery of threshold doses of lobeline and re-examining the two protocols a week after PMV, i.e. when pulmonary artery wedge pressure would have fallen. The hypothesis underlying this approach was that the level of sensory discharge in J (pulmonary C fibre) receptors in response to the dose of their specific chemical stimulant in experimental animals, varies with the prevailing pulmonary capillary pressure or pulmonary congestion (Paintal and Anand, 1992).

2. Methods

The study conformed to the Helsinki Declaration and was approved by the ethical committee of All India Institute of Medical Sciences (AIIMS), New Delhi, where it was carried out on patients with rheumatic mitral stenosis. Patients and their attendants were fully informed about the procedures that they would undergo and to this, all gave their consent. These involved assessing the nature of respiratory sensations (i) arising with a 6-min walk (ii) and in response to intravenously injected lobeline and (iii) restudying these in all patients a week after undergoing PMV.

2.1. Selection of subjects

Eight patients (2 males and 6 females) of rheumatic mitral stenosis who were due for a PMV intervention, were studied. The mean age of the group was 30 ± 7.6 years (S.E.M.), body weight, 43.3 ± 2.7 kg (S.E.M.) and height 154 ± 2.5 cm S.E.M. All were classified as belonging to NYHA Class III functional group (New York Heart Association: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th ed. Boston, MA: Little, Brown & Co., 1994:253–256).

2.2. Protocols

2.2.1. Lobeline study (injections and reporting sensations)

Lobeline-HCl (Sigma, USA) solution was prepared in normal saline (2 mg/ml) and injected through the right ante-cubital vein as a bolus. A day before they underwent PMV, the minimal dose of lobeline that the patients said produced a distinct sensation, was at first determined (the threshold dose). Thereafter, respiratory sensations were noted in response to gradually increasing ($\times 5$ μg/kg) doses delivered after an interval of at least 3 min till a dose produced a cough; each dose was given thrice without the patients being aware that it was the same dose so that its intensity could be determined accurately. The latter was assessed by means of Borg scale of 1–5, where intensity 1 was 'just noticeable' and 5 was equivalent to that presented by a supra threshold dose, but lesser than that which produced a cough. Normal saline (0.5 ml) injected into the same site served as the control or placebo.

Subjects were instructed to signal sensations that were felt in the mouth, throat and chest areas after injecting lobeline by means of a hand-held switch.

When asked to describe the nature of the sensations evoked, they referred to the following list of 10 sensations which included (1) need to take in more air (2) awareness of breathing rapidly (3) awareness of tightness in throat/chest with an inability to breathe due to it (4) suffocation/choking (5) dryness, irritation, heat in mouth or throat (6) pressure in nose, throat or chest of air/cold air/smoke (7) pain or burning in midsternal or epigastric area (8) need to cough or a cough (9) palpitations (10) any other (hiccups). Reticence was overcome by repeatedly drawing their attention to this list.

Lobeline injections were accompanied by a continuous record of thoraco-abdominal movements by means of a pneumograph connected to a Statham P23 Gb, on a Polyrite 4 recorder (Medicare Systems, India). Respiratory frequency (RF) was calculated from it as breaths per minute. A marker-channel recorded events when signalled by subjects.

2.2.2. Sensations with 6-min walk test

Using the American Thoracic Society guidelines (2002) patients were made to walk for 6 min in a long corridor, i.e. in an area where they were not slowed down because of sudden turns. All tests were carried out at the same time of the day, i.e. early afternoon with the indoor temperature maintained at 26 °C.

Before starting, the patients were given explicit instructions to stop as soon as they felt any kind of discomfort. They were also instructed that at the end of the walk they would have to recall if they detected anything at all (yes/no); the nature of the sensation (s)/feeling and whether they found it/them different or similar from the list of 10 sensations given earlier (see above).

2.2.3. Distance walked

At the end of the walk the distance covered in metres and the actual time utilized was noted down, as also were the sensations that they had reported.

Both protocols were repeated a week after patients underwent PMV.

2.3. PMV procedure and intracardiac pressure measurements

The valvulotomy procedure was carried out by the percutaneous transeptal approach using the Inoue balloon technique (Inoue et al., 1984). Right heart catheterisation using a Swan Ganz catheter (Size 7 French, Arrow) was used for haemodynamic measurements during PMV. Mitral valve area (cm^2) was estimated both before and after valvulotomy by the Gorlin formula (Gorlin and Gorlin, 1951). Cardiac output was estimated with the patient lying supine at the time of catheterisation by using the Fick principle both before and after the valvulotomy procedure.

2.4. Statistical analysis

A student's paired *t*-test was used for finding the significance of change before and after PMV for the lobeline dose (for threshold