Airway distensibility in healthy and asthmatic subjects: effect of lung volume history

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IT IS WELL ESTABLISHED that the dimensions of the airways and the anatomic dead space (Vd) increase with lung inflation (7, 21, 22, 30). The change in Vd with lung volume (ΔVd) has been proposed as a measure of the distensibility (or stiffness) of the airways (15, 31, 37), which may offer a useful test of airway function in asthma. However, only one study has compared this index between normal subjects and patients with asthma (37). This study found that ΔVd was reduced in mild asthmatic subjects [27.0 ± 8.8 (SD) ml/l] compared with nonasthmatic subjects [37.3 ± 8.8 (SD) ml/l]. The investigators speculated that this finding was a consequence of the structural changes or “remodeling” associated with airway inflammation, which is a feature of asthma (11). These structural changes include the deposition of scar-type collagen, smooth muscle thickening, and increased vascularity of the lamina propria (24, 36). It is possible, therefore, that ΔVd could provide a sensitive in vivo index of early structural changes in the airway wall that potentially precede the development of nonreversible airflow limitation.

The finding of less distensible airways in mild asthmatic subjects (37) was based on an unconventional method for estimating Vd (38) and has not been demonstrated by using the more widely accepted Fowler equal-area method for estimating Vd (15). The Fowler method provides a more rigorous measurement of Vd because it takes the shape of phase 2 and slope of phase 3 into account.

The observation of a reduced ΔVd in mild asthma (37) may reflect differences in the dynamics of the airway-parenchymal interdependence between groups. That is, as the lung is inflated, the expansion of the diseased and possibly stiffer airways lags behind that of the parenchyma. This suggests that ΔVd may be dependent on lung volume history. Evidence for this comes from observations that, at a given lung volume, normal airways dilate after a deep inhalation (16, 19, 20), but this response may be absent in asthmatic subjects (7, 8, 13). Therefore, if ΔVd is to be a useful index of the stiffness of the airways, its dependence on lung volume history needs to be assessed and, if necessary, consistent volume maneuvers need to be performed.

Most studies reporting the relationship between Vd and lung volume have used N2 as the indicator gas (15, 25, 30, 37). In these studies, a breathing circuit was used to deliver oxygen, and Vd was derived from the concentration of N2 at the lips (15). Therefore, these methods were restricted to the performance of a single measurement of Vd at a specific lung volume with a wash-in period of air breathing between measurements. To obtain an estimate of ΔVd, the measurement of Vd had to be repeated at a number of known lung volumes. These restrictions, which render the method time consuming, can be avoided when CO2 is used as the indicator. In this approach, the conducting airways are flushed with inspired air during tidal breathing, allowing Vd to be measured during expiration on a breath-by-breath basis, and ΔVd can be calculated after a period of tidal breathing at varying end-inspiratory lung volumes (EILV). Bartels et al. (4) have shown that Vd measured with CO2 is not significantly different from that obtained using N2.
Furthermore, there have been no studies investigating the relationship between $\Delta V_D$ and conventional indexes of body size and airway function such as forced expiratory volume in 1 s (FEV$_1$), forced vital capacity (FVC), FEV$_1$/FVC% [forced expired ratio (FER)], and forced maximal midexpiratory flow (FEF$_{25-75}$%). Such correlations may help in our understanding of this index of airway distensibility.

The aims of this study were 1) to develop and apply in healthy and asthmatic human subjects a rapid, tidal breathing CO$_2$ washout test for measuring $\Delta V_D$; 2) to determine its dependence on lung volume history; and 3) to determine any correlation with body size and conventional indexes of lung function.

**METHODS**

Subjects

Sixteen healthy subjects (controls) and sixteen mildly asthmatic subjects volunteered to participate in this study. The asthmatic subjects met the American Thoracic Society criteria for the diagnosis of asthma (1). Each subject attended the laboratory on two occasions within 7 days of each other. During the first visit, measurements of baseline ventilatory function and bronchial hyperreactivity to inhaled methacholine chloride (MCh) were performed. During the second visit, ventilatory function (pre- and postbronchodilator) and lung volumes were established before measurement of $V_D$ and $\Delta V_D$.

Physiological Measurements

All measurements were conducted with the subjects seated and wearing a nose clip. All volumes and flows were corrected to BTPS conditions.

FEV$_1$, FVC, FER, and FEF$_{25-75}$% were measured with a precalibrated computerized rolling seal spirometer (Sensor-Medics 2200) according to American Thoracic Society recommendations (2). The response to $\beta$-agonist was quantified in the asthmatic group 10 min after the administration of 200 $\mu$g albuterol via a metered-dose inhaler and spacer device. Total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) were measured postbronchodilator in a constant-volume whole body plethysmograph (PK Morgan) (10).

Doubling doses of MCh were administered with a breath-activated dosimeter until the FEV$_1$ fell $\geq 20\%$ from the baseline value (5). The dose of MCh causing a 20% fall in FEV$_1$ (PD$_{20}$) was calculated by linear interpolation. The test was performed only after asthmatic subjects had refrained from using albuterol for at least 8 h. Nonspecific antihistamines were not permitted in the 4 days before the challenge.

Anatomic $V_D$ and $\Delta V_D$

$V_D$ and EILV were measured with the apparatus illustrated in Fig. 1. Each subject breathed from a closed breathing circuit via a two-way valve (no. 1400, Hans Rudolph) attached to an 8-liter rolling seal spirometer (PK Morgan). CO$_2$ was scrubbed from the inspiratory limb of the breathing circuit by two soda lime canisters arranged in series. The CO$_2$ concentration at the lips was measured by using a rapidly responding infrared gas analyzer (Amatech CD-A3, Applied Electrochemistry). Respired volume and CO$_2$ concentration were stored on a personal computer for subsequent analysis.

For the measurement of $V_D$ and $\Delta V_D$, each subject breathed tidally on the apparatus from FRC via a mouthpiece for 1 min at 25 breaths/min. To minimize variations in $V_D$, all subjects sat upright and were instructed to hold their head erect with the lower orbital margin level with the external auditory meatus (4, 28). Each subject then performed the following tidal breathing maneuvers in random order with a 3-min interval between each (Fig. 2).

LMH regimen. For the low/medium/high (LMH) breathing regimen, each subject inhaled to TLC to establish the lung volume reference point and then was coached to breathe tidally for $\sim$30 s at near TLC. The subject then rested off the mouthpiece for 2 min. The experiment was then repeated at lung volumes near FRC and near RV. The order of TLC, FRC, and RV was randomized between subjects to prevent any possible systematic errors.

TLC-RV regimen. Each subject breathed tidally at FRC before inhaling to TLC (to establish the lung volume reference point) and then breathed tidally for 30 s at progressively diminishing lung volumes until RV was approached.

RV-TLC regimen. This breathing regimen was performed in a similar manner to the TLC-RV regimen, except that each subject first expired to RV (to establish the lung volume reference point) and then breathed tidally with progressively increasing lung volume to TLC.

The lung volume corresponding to each measurement of $V_D$ was determined by subtracting the total volume exhaled from TLC (TLC-RV and LMH regimens) or by adding the volume inspired from RV (RV-TLC regimen). The TLC-RV and RV-
TLC regimens were performed in triplicate to obtain sufficient data points for the determination of $D_V$. While subjects performed the breathing regimens, a tidal volume (VT) of at least 0.4 liters was encouraged to ensure that the conducting airways were adequately flushed with air during inspiration and that an adequate alveolar plateau (phase 3, Fig. 3) was recorded during each expiration. For visual feedback, the breathing maneuver was displayed to the subject on an oscilloscope as a plot of respired volume against time. To minimize the chance of transient breath holding during tidal breathing, all experiments were carried out at a breathing frequency of 25 breaths/min, established by the subject breathing in time with a metronome.

The measurements of $V_D$ were obtained from the expiratory portion of each tidal breath (CO$_2$ vs. volume; Fig. 3) recorded during each breathing regimen by the equal-area method (15). The apparatus $V_D$ (14 ml) was subtracted from each measurement of $V_D$, and then the volume was corrected to BTPS conditions. Breaths were excluded from analysis if they showed an end-inspiratory pause (>0.3 s), if VT was <0.4 liters, or if the slope of phase 3 could not be confidently estimated.

Statistical Analysis

All results are expressed as means ± SE. The significance of the mean difference between and within the control and asthmatic groups for $V_D_{50%}$, $V_D_{50%/TLC}$, and $D_V$ was determined by ANOVA. Linear regression analysis and Pearson's product-moment correlation coefficient were used to determine whether $V_D_{50%}$ and $D_V$, using the TLC-RV regimen, were significantly related to age, stature, weight, and indexes of lung function (absolute values and percent predicted). The repeatability of $V_D_{50%}$ and $D_V$ for each of the three breathing regimens was assessed in four of the control subjects by repeating their measurements on 3 separate days.

RESULTS

Subjects

The two study groups were well matched for stature, gender, and body mass index (BMI; see Table 1). However, the asthmatic group was 10.5 yr older than the control group. The control subjects had normal ventilatory function and lung volume, and none was hyperresponsive to MCh (PD$_{20}$ > 2 mg). The asthmatic subjects had mild airflow limitation (prebronchodilator FER = 66%, postbronchodilator FER = 73%) and were
Lung function indexes are given as absolute value with percentage predicted (9) value in parentheses. BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FER, forced expired ratio (FEV1/FVC%); FEF25–75%, forced maximal midexpiratory flow; PD20, dose of methacholine chloride causing a 20% fall in FEV1; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume.

Subjects’ Performance of the Anatomic VD Test

All subjects were able to satisfactorily perform the breathing maneuvers required for the measurement of VD and ΔVD using the LMH and TLC-RV breathing regimens. Approximately 50% of the subjects were able to perform these two breathing maneuvers satisfactorily on their first attempt. The remaining subjects required one, or at most two, practice attempts before technically satisfactory results were obtained. All subjects found the RV-TLC regimen the most difficult to perform, particularly when attempting to breathe tidally near RV, having first exhaled completely. Five asthmatic subjects and one control subject were unable to satisfactorily complete this regimen; results were obtained in 11 and 15 subjects, respectively. The average time to complete each breathing regimen in triplicate was 15 min (maximum time was 35 min).

The mean number of VD measurements for all breathing regimens per subject used to determine ΔVD was 21.1 ± 0.9 for the control group and 21.7 ± 1.4 for the asthmatic group.

On average, one tidal breath in 33 was rejected; most of these were the first breath due to the presence of an end-inspiratory pause or low Vt (<0.4 liter). The number of breaths rejected was similar for the control (0.6 breaths per subject) and asthmatic (0.7 breaths per subject) groups.

VD, Expired Flow, Breathing Frequency, and Slope of Phase 3

For all breathing regimens, the mean expired Vt obtained during the measurement of VD was not significantly different between the control (1.01 ± 0.33 liter) and asthmatic (1.07 ± 0.30 liter) groups. The mean expired flow for each tidal breath was also similar between groups at 0.76 ± 0.21 and 0.75 ± 0.17 l/s for the control and asthmatic groups, respectively. The mean breathing frequency was slightly lower than the target value of 25 breaths/min at 24.2 ± 0.3 and 23.4 ± 0.4, respectively. The slope of phase 3 decreased with increasing lung volume to similar extents in both groups (Fig. 4).

Repeatability of VD50% and ΔVD

The TLC-RV regimen was the most repeatable with a mean CV of 7.1% for VD50% and 9.1% for ΔVD. The RV-TLC regimen was the least repeatable with a mean CV of 10.1% for VD50% and 13.1% for ΔVD.

There were no significant differences in VD50% or ΔVD50% adjusted for TLC (Vd50%/TLC) among the three breathing regimens either within or between subject groups. For the control and asthmatic groups, respectively, the mean VD50% was 130.8 ± 8.3 and 141.3 ± 6.1 ml for the TLC-RV regimen, 128.5 ± 8.4 and 135.1 ± 6.8 ml for the LMH regimen, and 130.5 ± 7.2 and 140.1 ± 5.9 ml for the RV-TLC regimen.

ΔVD

ΔVD was significantly different between the two study groups for each of the LMH and TLC-RV regimens but not for the RV-TLC breathing regimen (see Table 2). However, for the RV-TLC regimen, there was also a trend for a lower ΔVD in the asthmatic group. Within each subject group, ΔVD was not significantly different among breathing regimens.

Figure 5 shows the raw data obtained in one asthmatic and one control subject for the three breathing modes.
regimens. The plots demonstrate that the relationships are approximately linear for each breathing regimen.

Correlation of $VD_{50\%}$ and $\Delta Vo$ with Age, Body Size, and Lung Function

$VD_{50\%}$. For the control group, significant correlations were found between $VD_{50\%}$ and height ($P = 0.02$), FVC ($P = 0.005$), TLC ($P = 0.05$), FRC ($P = 0.005$), and RV ($P = 0.006$). In the asthmatic group, significant correlations were found between $VD_{50\%}$ and height ($P = 0.02$), $PD_{20}$ ($P = 0.05$), TLC ($P = 0.01$), and RV ($P = 0.04$). The relationship between $VD_{50\%}$ and $PD_{20}$ became insignificant when $VD_{50\%}$ was adjusted for TLC. Significant correlations were not found between $VD_{50\%}$ and the absolute change in FEV$_1$ or FEF$_{25–75\%}$ after the administration of albuterol. Significant correlations were not found between $VD_{50\%}$ and age, weight, or BMI.

$\Delta Vo$. No significant correlations were found in the control group between $\Delta Vo$ and height, weight, height, BMI, or lung function. In the asthmatic group, significant correlations were found between $\Delta Vo$ and prebronchodilator FER, FEF$_{25–75\%}$ and FEF$_{25–75\%}$ expressed as percent predicted and also between $\Delta Vo$ and postbronchodilator FER, FEF$_{25–75\%}$ and RV expressed as percent predicted (Table 3). Significant correlations were not found in the asthmatic group between $\Delta Vo$ and the absolute or percent change in FEV$_1$ or FEF$_{25–75\%}$ after the administration of albuterol.

**DISCUSSION**

We have developed a rapid, repeatable, and easily used CO$_2$-washout method for measurement of $Vo$ and $\Delta Vo$ with lung volume. This has distinct advantages...
Table 3. Significant correlations of ∆VD (TLC-RV regimen) with lung function in asthmatic subjects

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%pred, Percent predicted.

over a previously described method based on N₂ washout (15, 37). From a practical point of view and in terms of reproducibility of VD₅₀% and ∆V₀, the TLC-RV regimen was the method of choice, being the easiest to perform and producing the least variability.

This study has shown that the airways of mildly asthmatic subjects (postbronchodilator) have a similar luminal volume when measured near FRC (VD₅₀%) but are less distensible than normal airways, thus confirming a study using a single-breath N₂-washout method (37). The reduced ∆V₀ of the asthmatic group is consistent with the widely accepted view that a primary defect in asthma is a stiffened airway with the inability to passively dilate normally (14, 17). The significant correlations found in the asthmatic group between VD₅₀% and RV and FEF 25–75%, suggest that ∆V₀ is associated with the distension of peripheral rather than proximal airways. It was also shown that lung volume history had little effect on the measurement of VD₅₀% or ∆V₀ in either group.

Anatomic V₀

The similar results for VD₅₀% for the three breathing regimens both within and between subject groups indicated that the volume of the airways at 50% TLC was not affected by lung volume history.

This finding was unexpected because lung volume history has been shown to increase V₀ by a mean of 8% when measured at a given lung volume after inflation to TLC compared with measurements made after exhalation to RV (18). In contrast, in mild asthma, V₀ measured at FRC, decreased by 7–10% after inflation to TLC (8). These reported opposite responses to a deep inflation in healthy and asthmatic subjects suggest that the mechanical interdependence of the airways and parenchyma may have been different in that healthy airways have a greater degree of hysteresis compared with the lung parenchyma and vice versa in asthma. There are several possible explanations for our finding that VD₅₀% was not different between groups for the three breathing maneuvers. 1) The asthmatic group was assessed after the administration of albuterol. This was done to reduce regional ventilation inhomogeneity, because it has been shown that V₀ can be underestimated if lung units with long time constants contribute their V₀ to phase 3 (25). 2) Because the breathing regimens used in this study were primarily designed to allow the rapid measurement of ∆V₀, they differed from those used previously (8, 16) in that our VD₅₀% data were obtained during tidal breathing commencing immediately after a single inspiration to TLC (LMH and TLC-RV regimens) or exhalation to RV (RV-TLC regimen). However, in these previous studies, V₀ was measured immediately after four or five maximal inhalations to TLC (8, 16). These differences in volume history may have affected the viscoelastic properties of the airways and parenchyma; it has been clearly shown that the effect of lung volume history is time dependent with the maximal response occurring immediately and decaying rapidly thereafter (18, 29). However, it is of interest that our V₀ data using the LMH regimen in which measurements were made immediately after a single inspiration to TLC (8, 16). These differences in volume history may have affected the viscoelastic properties of the airways and parenchyma; it has been clearly shown that the effect of lung volume history is time dependent with the maximal response occurring immediately and decaying rapidly thereafter (18, 29).

The finding that, when CO₂ was used as the indicator gas and the equal-area method was applied, VD₅₀% was not significantly different between the control and mildly asthmatic subjects extends previous work (37). The similar values for VD₅₀% suggest that the airways of mild asthmatic subjects, at least postbronchodilator, are not uniformly narrower than normal. The only other explanation is that the alveolar-airway interface was located in more peripheral airways in asthmatic subjects compared with control subjects; that is, a peripheral movement of the interface offsets narrowed airways proximal to it.

∆V₀

The lower values for ∆V₀ in asthmatic subjects suggests that their airways were stiffer than normal. This finding adds to the study by Wilson et al. (37), who reported mean values for ∆V₀ using N₂ and the Young (38) method for computing V₀ of 37.3 ± 8.8 ml/l in control and 27.0 ± 8.8 ml/l in mildly asthmatic subjects. However, the values reported in those studies were higher than the values reported here. This was unlikely to be due to the use of CO₂ as the indicator gas because the diffusivity of this gas is only slightly less than N₂ (4). Our values for VD₅₀% in control subjects were similar to published values measured at a similar lung volume (15, 25). Similarly, our values for ∆V₀ in control subjects (24.3 ± 1.69 ml/l for the TLC-RV regimen) are similar to previously published values: 24 ml/l (25) and 30 ml/l (35).

Of interest was the finding that, in the RV-TLC regimen, ∆V₀ was not significantly different between our two subject groups, although there was a trend in the same direction as with the other regimens. This result may reflect a type-2 error due to the reduced number of subjects tested with this regimen (n = 11).
However, it could also reflect a lung volume history effect. The reduced $\Delta V_d$ of the asthmatic group cannot be explained on the basis of differences between groups in expired flow, breathing frequency, $V_t$, or slope of phase 3. The decrease in the slope of phase 3 with increasing lung volume, which was a feature in both groups (Fig. 4), would have affected the calculated $V_d$, producing a slightly larger measured value at TLC (28). This is because the equal-area method used to compute $V_d$ requires the extrapolation of phase 3, which affects the measurement of $V_d$. Thus the decrease in slope would be expected to have affected $\Delta V_d$ to similar extents in both groups. Also, any systematic errors due to the choice of indicator gas or other methodological differences would also be applicable in both study groups and are, therefore, unlikely to have affected the comparison of $\Delta V_d$ between groups.

Although there is substantial evidence that the dimensions and volume of the airways increase with lung inflation (7, 21, 22, 30), it has not been conclusively demonstrated that the index, $\Delta V_d$, directly reflects these changes. Other than airway dilatation, the following mechanisms may explain or contribute to the lower $\Delta V_d$ in asthma.

Alveolar-airway interface being displaced peripherally with lung inflation more in normal subjects than in asthmatic subjects. The alveolar-airway interface, however, has been shown to be affected by airway geometry such that it is always located in similarly sized airways (12, 30). At low lung volumes, one would expect the interface to move relative to proximally as the small airways narrow, and this effect may be slightly more pronounced in the asthmatic group because of the presence of some residual excessive airway narrowing. A lower $V_d$ at low lung volumes in asthma should tend, if anything, to give a steeper slope for $\Delta V_d$ rather than what was found.

Recruitment of airways at high lung volumes, more in normal than in asthmatic subjects. If airway recruitment played a role, it is unlikely that the following would have been observed: 1) lower-than-normal $V_d$ near TLC in asthma or 2) similar values for the slope of phase 3, suggesting that there were similar degrees of ventilatory inhomogeneity between subject groups. Airway recruitment would also be expected to occur to a greater extent in the asthmatic group due to the presence, albeit marginally in our bronchodilator-treated subjects, of airflow limitation. Thus airway recruitment would have produced a larger rather than smaller $\Delta V_d$ in asthma if this were a confounder.

Asynchronous pattern of lung emptying due to irregular airway branching with far shorter path lengths to alveoli in the apical zones than at the bases. Pleural pressure is also topographically distributed because of the weight of the underlying lung (33, 34). Thus at any given lung volume the apical airways are subjected to a greater distending pressure than those in the bases. The effect of this pattern on regional airway size is greatest at low lung volumes (3). This results in an asynchronous pattern of lung emptying with apical airways emptying faster than those in the bases, and it is possible that part of the dead space volume of some airways would not be included in the measured $V_d$ if they were not fully flushed with alveolar gas before the establishment of the alveolar plateau. The volume of “lost” $V_d$ is likely to depend on the level of lung inflation, with the greatest “loss” in $V_d$ occurring at low lung volumes. Thus part of the index, $\Delta V_d$, may result from this mechanism and may account, at least in part, for the lower value observed in asthma.

The linear relationship between $V_d$ and lung volume (Fig. 5) is inconsistent with the model of a stiff epithelial basement membrane (23) that limits distension unless significant folding and buckling of the airway wall was present, such that unfolding occurred throughout the range of lung volume studied. If unfolding were complete before TLC was reached, then we would expect $V_d$ not to have continued to increase in a linear fashion as observed but to have reached a plateau. This conclusion is consistent with the results of a study in dogs that used high-resolution computer tomography to measure airway size (7). In this study, the effect of lung volume on airway diameter was measured after the administration of atropine to reduce airway tone or MCh to increase tone. Airways with reduced tone were found to distend easily up to a relatively low transpulmonary pressure of 5–7 cmH$_2$O with no further distension at higher pressures. In contrast, airways with increased tone distended at varying rates up to full lung inflation. Presumably the airways in both our groups had sufficient muscle tone to fit with the latter model.

The linear change in $V_d$ with lung volume also fits with the model that both alveoli and airways expand together in proportion to the linear change in depth of the thorax or as the cube root of lung volume (7, 21, 22). The airways also lengthen with lung inflation; however, this has been reported not to affect airway volume (22). Because $\Delta V_d$ was lower in our asthmatic group, however, the effect of the distending force on the airway wall appears to be less than in our normal subjects.

Correlation of $V_d$ with Age, Body Size, and Lung Function

The positive relationships in the control group between $V_d$ with height, TLC, FVC, FRC, and RV agree with previous findings (9, 28) that the volume of the airways is related to body and lung size. On the basis of lung size, we would have also expected a significant relationship between $V_d$ and FEV$_1$ in the control group because both are positively related to TLC. However, no relationship was found, suggesting either that the range of values obtained in our subjects was too limited or that the number of subjects included in these studies was insufficient. Also of interest was the negative relationship in asthma between $V_d$ and PD$_{20}$, indicating that the more responsive asthmatic subjects had a larger $V_d$ when fully bronchodilated, which was seen as intuitively paradoxical. However, because this relationship disappeared when $V_d$ was adjusted for TLC, it is most likely that the more
reactive asthmatic subjects coincidentally had lower TLC values. The correlation between ΔV0 and RV (percent predicted) in asthma suggests that those subjects who were able to exhale to low lung volumes have more distensible airways, presumably also due to the absence of significant peripheral airway disease.

In conclusion, this study has shown that our newly developed tidal breathing, CO2-washout method for measuring V0 and ΔV0 was easily and rapidly performed by untrained subjects. The change in V0 with lung volume was found to be less in the mildly asthmatic subjects, indicating that their airways were stiffer than normal and that this was not obviously affected by lung volume history. The positive correlation of ΔV0 with RV and FEF25–75% suggests that the peripheral airways were abnormally narrow and that this was associated with reduced airway distensibility. It was speculated, therefore, that the peripheral airways represent the major site of airway distension.

We thank C. Ingram and S. Augustin for technical assistance, M. Gorman for assistance with the computer program, and M. Bailey for statistical advice. We also thank Dr. X. Li and Dr. M. Pain for valuable comments throughout the study.

This study was supported by the National Health and Medical Research Council of Australia and GlaxoWellcome Australia.

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Received 5 April 1999; accepted in final form 30 November 1999.

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