

# Ventilatory Requirements of Critically Ill Neonates

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Ventilatory requirement was assessed in 15 critically ill neonates on a total of 31 occasions. All were either currently receiving mechanical ventilation or had had mechanical ventilation in the recent past. Minute ventilation, respiratory frequency, carbon dioxide production ( $\dot{V}_{CO_2}$ ) and arterial blood  $P_{aCO_2}$  were measured. Dead space-to-tidal volume ratios ( $V_D/V_T$ ) were calculated. The ventilatory requirements of the infants ranged from 1.16 to 4.30 times normal. Derived parameters related the increased ventilatory requirement to pulmonary ( $V_D/V_T$ ) and metabolic ( $\dot{V}_{CO_2}$ ) factors. The increased requirement was not significantly related more often to either of these two factors, although one or the other was frequently predominant in individual cases. Data presented allow specification of the minute volume range needed for ventilators designed for neonates, and the maximal compressible volume that can be tolerated when expired volume monitoring is desired. (Key words: Anesthesia, pediatric. Carbon dioxide, production. Equipment, ventilators. Monitoring, ventilation. Ventilation: dead space; mechanical.)

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THE WIDE AVAILABILITY of constant-volume mechanical ventilators for adult patients and the relative ease of measuring expired volume and carbon dioxide have allowed the clinician to use parameters such as dead space-to-tidal volume ratio, ventilatory requirement, and metabolic (carbon dioxide) load in the routine management of adult patients in respiratory failure. This has not been the case for infants needing artificial ventilation. In the first instance, a volume-limited ventilator with an internal compliance or compressible volume small enough to allow accurate prediction or measurement of tidal volume is simply not available.<sup>1</sup> Moreover, even if one wished to devote the resources needed to produce a volume-limited ventilator for neonates, information concerning the minute ventilation requirements of neonates with diseased lungs and deranged metabolic status is insufficient to allow formulation of the required design criteria. In order to provide information needed for the design of such a ventilator, we report the minute ventilation requirements of critically ill neonates during mechanical ventilation. We also report the relative contributions of the inefficiency of gas exchange (dead space) and the metabolic load ( $CO_2$  production) to this ventilatory requirement.

## Methods

### PATIENT SELECTION

Thirty-one studies were done on 15 randomly selected neonates in respiratory failure who at some stage of their disease needed mechanical ventilation. Seven of the patients had idiopathic respiratory distress syndrome, while the remainder represented a wide range of diseases seen in neonates. The median age at the time of study was 4 days (range 0.8 to 74), and the median weight 2.2 kg (range 0.92 to 3.15). The neonates were studied during spontaneous ventilation (nine studies) or during mechanical ventilation at the clinically indicated rate, minute volume, and end-expiratory pressure (22 studies). Ventilator settings were not changed for the purpose of this investigation. Of the 15 patients, eight died during hospitalization.

### PHYSIOLOGIC MEASUREMENTS AND VENTILATOR EMPLOYED

In all patients, arterial blood  $P_{CO_2}$ , expired minute ventilation ( $\dot{V}_E$ ), and expired carbon dioxide ( $FE_{CO_2}$ )

### SYMBOLS

$C_v$	Compliance of ventilator circuit
$f$	Respiratory frequency
$FA_{CO_2}$	Fraction of carbon dioxide in alveolar air
$FE_{CO_2}$	Fraction of carbon dioxide in expired air
$K$	A constant ( $K = [P_B - PA_{H_2O}]36$ )
$L(CO_2)$	Dimensionless parameter determining ventilatory load due to metabolic (carbon dioxide production) factors: $L(CO_2) = \dot{V}_{CO_2}/\text{normal } \dot{V}_{CO_2}$
$L(V_D/V_T)$	Dimensionless parameter determining ventilatory load due to pulmonary (dead space) factors: $L(V_D/V_T) = \frac{1 - \text{normal } V_D/V_T}{1 - V_D/V_T}$
$Pa_{CO_2}$	Partial pressure of carbon dioxide in arterial blood
$PA_{CO_2}$	Partial pressure of carbon dioxide in alveolar air
$PA_{H_2O}$	Partial pressure of water in alveolar air
$P_B$	Barometric pressure
$P_E$	Pressure in ventilator circuit at end of expiration
$P_I$	Pressure in ventilator circuit at end of inspiration
$V_C$	Volume lost due to compression in ventilator circuit: $V_C = (P_I - P_E) \cdot C_v \cdot f$
$\dot{V}_{CO_2}$	Volume of carbon dioxide expired per minute
$V_D$	Physiologic dead space
$\dot{V}_E$	Minute volume
$\dot{V}_N$	Minute volume normalized for $Pa_{CO_2}$ ( $V_N = V_E \times \frac{36}{Pa_{CO_2}}$ )
$V_T$	Tidal volume

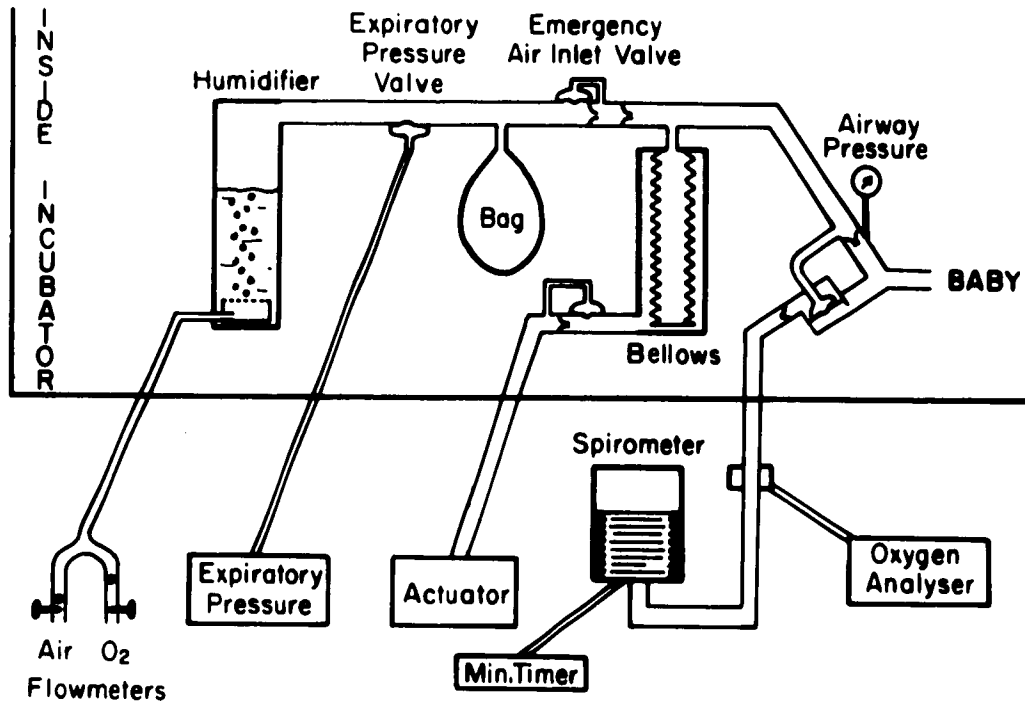


FIG. 1. Ventilator used. See text for functional description.

were measured. All measurements were made as part of routine patient care. Blood was withdrawn from an indwelling umbilical arterial catheter for measurement of  $P_{aCO_2}$ . Previous investigators have found it difficult or impossible to measure  $\dot{V}_E$  and  $F_{E_{CO_2}}$  in neonates during routine mechanical ventilation because the gas exiting from the expiratory valve of the ventilator has, in general, two sources. The first is the "true" expired gas from the patient; the second is gas that had been compressed in the ventilatory circuit during inspiration. The magnitude of this latter "compressed volume" is equal to the product of the difference between the end-inspiratory ( $P_I$ ) and end-expiratory ( $P_E$ ) pressures and the compliance ( $C_V$ ) of a section of the ventilator circuit. The magnitude of this compliance is usually in the range of 3–6 ml/cm  $H_2O$  with ventilators designed for adults.<sup>2</sup> Even with a commercially available ventilator specifically designed for neonates, such as the Bourns LS 104–150, the  $C_V$  is reduced to 0.5 ml/cm  $H_2O$  at best. The volume compressed can be quite large. For example, for an inspiratory pressure of 40 cm  $H_2O$  and an expiratory pressure of 0 cm  $H_2O$ , the volume compressed, assuming a  $C_V$  of 0.5 ml/cm  $H_2O$ , is 20 ml. Thus, when a neonate is ventilated, the major fraction of gas exiting from the expiratory valve is, in fact, not expired gas. Because of errors in estimating ventilator pressures and  $C_V$ , it has not previously been possible routinely to determine expired volume (and expired carbon dioxide concentration) accurately.

We have been able to collect expiratory gases virtually undiluted by compressed gas by use of a ventilator circuit of extremely low volume (fig. 1). The ventilatory circuit and nonbreathing valves are modified from those described by Frumin, Lee, and Papper.<sup>3,4</sup> An exceedingly low compressible volume has been achieved by the use of short, narrow-bore (3/16 inch I.D.) tubing, location of the nonbreathing valve close to the patient, as suggested by Haddad and Richards,<sup>5</sup> and, most importantly, by removal of the humidifier from the patient circuit. Water is added as a gas by placing the humidifier between the fresh-gas flowmeters and the bellows. Since the humidifier is outside the patient circuit, the relatively large volume of air it contains, which varies with the water level, does not contribute to the compressible volume.<sup>5</sup> The entire ventilator is heated with warm air (or placed within the incubator) so as to provide adequate humidification while avoiding condensation in the bellows and tubing and on the valves. The ventilator compliance was measured using procedures suggested in ANSI standard Z79-1976 and found to be 0.03 ml/cm  $H_2O$ .<sup>6</sup> Thus, at 40 cm  $H_2O$  inspiratory pressure, the volume error due to compression, if uncorrected, would be 1.2 ml per breath, or about one order to magnitude less than the tidal volume of a neonate. The lack of condensation avoids "sticky" valves and makes spontaneous breathing from the reservoir bag with or without continuous positive pressure practical. Intermittent positive pressure is provided by an actu-

ator functioning as a variable-phase, constant-flow generator, which compresses the bellows. Because of the low total system volume, it can be predicted that the actual flow at the infant's airway will approximate the actuator's waveform.<sup>2</sup> We had used this ventilator for the routine care of more than 50 neonates during the three-year period preceding the present study.

DATA ANALYSIS

Expired gas was collected for 10 minutes and the volume measured in a water-seal spirometer. Respiratory rate was counted. The ventilator pressure was measured with the aid of a strain-gauge transducer (although because of the very low system compliance, a less precise aneroid manometer could have been used).

For data analysis, the measured spirometric volume was first corrected for the compressed volume ( $V_C$ ) by subtracting from it the product of number of breaths,  $(P_1 - P_E)$ , and  $C_V$ , and dividing the result by the number of minutes. The resulting minute ventilation volume was then corrected for BTPS. Only such corrected data are presented.

We calculated  $\dot{V}_{CO_2}$  by multiplying the measured spirometric volume (normalized to 1 minute and corrected for BTPS) by the  $CO_2$  concentration of this (well-mixed) gas. The  $CO_2$  concentration was determined by use of a calibrated infrared analyzer. By dividing  $\dot{V}_{CO_2}$  by the corrected minute ventilation ( $\dot{V}_E$ ),  $F_{ECO_2}$  was calculated. Then, using the Enghoff modification of the Bohr equation, we determined  $V_D/V_T$ .<sup>7</sup>

In order to understand the genesis of the ventilatory requirement, we derived a dimensionless parameter reflecting the total increase in ventilatory requirement and another reflecting the ratio of the increase attributable to pulmonary factors to that due to metabolic factors.

The relation of expired volume, dead space, and  $CO_2$  production is implicit in the Bohr equation for  $CO_2$ :

$$V_D/V_T = (F_{ACO_2} - F_{ECO_2})/F_{ACO_2} \quad (1)$$

Since:

$$\dot{V}_{CO_2} = F_{ECO_2} \times \dot{V}_E \quad (2)$$

and:

$$F_{ACO_2} = Pa_{CO_2}/(P_B - P_{AH_2O}) \quad (3)$$

(assuming  $Pa_{CO_2} = Pa_{CO_2}$ )

Equation 1 can be rewritten as:

$$\dot{V}_E/kg = \left[ \frac{1}{1 - V_D/V_T} \right] \cdot [\dot{V}_{CO_2}/kg] \times \left[ \frac{1}{Pa_{CO_2}} \right] \cdot [P_B - P_{AH_2O}] \quad (4)$$

The first term to the right of the "equals" sign is related to the efficiency of the lungs. The second term is dependent on the metabolic state. The third term, while dependent on ventilatory drive and muscle strength in the spontaneously breathing patient, can be set arbitrarily in patients receiving controlled mechanical ventilation. The fourth term is a constant.

As a first step in isolating the metabolic- and pulmonary-dependent factors, we normalized for  $CO_2$  levels. Since within a narrow range of  $Pa_{CO_2}$  values around normal ( $Pa_{CO_2} = 36$  torr), the minute ventilation is inversely proportional to  $Pa_{CO_2}$ , we defined  $\dot{V}_N$ , the  $CO_2$ -normalized ventilation, as:

$$\dot{V}_N = \dot{V}_E \times (Pa_{CO_2}/36) \quad (5)$$

This procedure leads to an error in determination of  $\dot{V}_N$ . Strictly speaking, this normalization is fully justified only for the component of minute volume representing alveolar ventilation. It also is reasonably accurate for the component representing alveolar dead space, as within reasonable limits it is proportional to tidal volume.<sup>8</sup> However, the anatomic dead-space component of the ventilatory requirement increases only a relatively small amount with increased ventilation.<sup>8</sup> Since, in most of our patients,  $V_D/V_T$  was abnormally high, and since our mean  $Pa_{CO_2}$  was not far from 36 torr (table 1), we consider the error introduced to be small, and an unavoidable result of our not changing the rate and volume for the purpose of this study. This normalization of  $\dot{V}_E$  does not, however, affect the load factors,  $L(CO_2)$  and  $L(V_D/V_T)$  (see below).

Combining equations (5) and (4):

$$\dot{V}_N/kg = \left[ \frac{1}{1 - V_D/V_T} \right] \cdot [\dot{V}_{CO_2}/kg] \cdot [K] \quad (6)$$

where K is a constant.

TABLE 1. Physiologic Data

	f (bpm)	P <sub>i</sub> (torr)	P <sub>e</sub> (torr)	V <sub>c</sub> (ml)	$\dot{V}_E$ (ml/min)	V <sub>T</sub> (ml)	$\dot{V}_{CO_2}/kg$ (ml/min)	$\dot{V}_E/kg$ (ml/min)	V <sub>T</sub> /kg (ml)	V <sub>D</sub> /V <sub>T</sub>	Pa <sub>CO<sub>2</sub></sub> (torr)
Mean	51	19	1.6	0.5	601	12.1	6.6	295	6.0	.53	40
SD	13	14	1.9	0.4	225	4.4	1.5	77	1.6	.11	7

TABLE 2. Derived Dimensionless Parameters

	$\dot{V}_N/\text{kg}$ (ml/min)	$L(V_D/V_T)$	$L(\text{CO}_2)$	$L(V_D/V_T) \times L(\text{CO}_2)$	$L(V_D/V_T)/L(\text{CO}_2)$
Mean	325	1.63	1.31	2.08	1.20*
SD	94	0.56	0.29	0.59	

\* Log transform used (see text).

For the case of normal  $V_D/V_T$  and normal  $\dot{V}_{\text{CO}_2}$ , the normal  $\dot{V}_N/\text{kg}$  can be expressed as:

Normal  $\dot{V}_N/\text{kg} =$

$$\left[ \frac{1}{1 - \text{normal } V_D/V_T} \right] \cdot [\text{normal } \dot{V}_{\text{CO}_2}/\text{kg}] \cdot [K] \quad (7)$$

Dividing equation (6) by equation (7) yields:

$$\frac{\dot{V}_N/\text{kg}}{\text{Normal } \dot{V}_N/\text{kg}} = \left[ \frac{1 - \text{normal } V_D/V_T}{1 - V_D/V_T} \right] \cdot \left[ \frac{\dot{V}_{\text{CO}_2}/\text{kg}}{\text{normal } \dot{V}_{\text{CO}_2}/\text{kg}} \right] \quad (8)$$

Defining the ventilatory load due to pulmonary factors,  $L(V_D/V_T)$ , as the first term to the right of the identity and the ventilatory load due to metabolic factors,  $L(\text{CO}_2)$ , as the second term yields:

$$\frac{\dot{V}_N/\text{kg}}{\text{Normal } \dot{V}_N/\text{kg}} = [L(V_D/V_T)] \cdot [L(\text{CO}_2)] \quad (9)$$

For the purposes of numerical evaluation, the normal  $V_D/V_T$  was taken to be 0.30, and the normal  $\dot{V}_{\text{CO}_2}/\text{kg}$ , 5.0 ml/kg/min.<sup>9-11</sup> For each study, the product of these loads,  $L(V_D/V_T) \times L(\text{CO}_2)$ , was used as an index of the excess ventilatory requirement. The quotient of these loads,  $L(V_D/V_T)/L(\text{CO}_2)$ , was used to determine their relative importances.

The mean and standard deviation were used to characterize parameters such as  $\dot{V}_N/\text{kg}$ ,  $L(V_D/V_T)$ ,  $L(\text{CO}_2)$ , and  $L(V_D/V_T) \times L(\text{CO}_2)$ . To determine the relative importances of  $L(V_D/V_T)$  and  $L(\text{CO}_2)$ , the central value of the ratio of  $L(V_D/V_T)$  and  $L(\text{CO}_2)$  was investigated. Ratios greater than 1.0 indicate that  $L(V_D/V_T)$  is more important; ratios less than 1.0 indicate that  $L(\text{CO}_2)$  is more important. To avoid biasing the mean towards quotients greater than 1, a logarithmic transformation of the data was first done, and the mean and standard deviation of the transformed data determined. For ease of data display, the inverse transformation of the mean was then done. Student's *t* test was used to determine whether the ratio differed significantly from 1.0 by testing whether the mean of the log-transformed data differed from 0.0. To provide a

check on this method, the significance was also tested by use of the "sign" test.<sup>12</sup> To determine whether  $L(V_D/V_T)$  correlated with  $L(\text{CO}_2)$ , a scattergram of the data was prepared, the correlation coefficient calculated, and the coefficients of the best-fit straight line determined for both untrimmed and trimmed data.

## Results

Tables 1 and 2 and figure 2 summarize the physiologic data.† The compressed volumes averaged 0.5 ml/ breath, and none was more than 12 per cent of the true tidal volume. The mean minute ventilation per kilogram ( $\dot{V}_E/\text{kg}$ ), corrected for compressed volume, was 295 ml/min, with a standard deviation of 77 ml/min. As  $\text{Pa}_{\text{CO}_2}$  was generally near 36 torr, normalization of  $\dot{V}_N$  for  $\text{Pa}_{\text{CO}_2}$  has little effect. The mean  $\dot{V}_N/\text{kg}$  was 325 ml/min, with a standard deviation of 94 ml/min. The range of values obtained for  $\dot{V}_N/\text{kg}$  was quite large (181–594 ml/min). The mean  $\dot{V}_{\text{CO}_2}$  was  $6.6 \pm 1.5$  ml/kg/min, with a range of 4.1 to 9.1 ml/kg/min. These resulted in a mean  $L(\text{CO}_2)$  of  $1.31 \pm .29$  (range 0.84–1.89). The mean  $V_D/V_T$  was  $0.53 \pm 0.11$ , with a range of 0.33 to 0.81. This resulted in a mean  $L(V_D/V_T)$  of  $1.63 \pm 0.56$ .

Figure 2 shows the relation between  $L(V_D/V_T)$  and  $L(\text{CO}_2)$  for the individual studies. The two parameters were poorly correlated. The correlation coefficient was 0.38 ( $P = 0.05$ ). When the data were trimmed to remove the five studies for which  $L(V_D/V_T)$  was greater than 2.0, which may have come from a separate population, the correlation coefficient decreased to 0.29 ( $P > 0.05$ ). The best-fit regression line had a marginally significant negative slope (slope =  $-0.74$ ,  $P = 0.05$ ), but after trimming, the slope was marginally significant but positive (slope =  $+0.26$ ,  $P = 0.05$ ), reflecting the fact that the data were poorly correlated.

The mean product of  $L(V_D/V_T)$  and  $L(\text{CO}_2)$ , reflecting the total increased ventilatory load, was 2.08. However, the required ventilation was as great as 3.52 times normal and was never less than normal.

Analysis of the ratio of  $L(V_D/V_T)$  and  $L(\text{CO}_2)$  showed that neither factor is, in general, predominant. The mean ratio was 1.20, which is not significantly dif-

† Detailed clinical and physiologic data for each patient have been filed with NAPS. See NAPS Document No. 03688 for eight pages of supplementary material. Order from ASIS/NAPS, c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10017. Remit in advance for each NAPS accession number. Institutions and organizations may use purchase orders when ordering, however, there is a billing charge for this service. Make checks payable to Microfiche Publications. Photocopies are \$5.00. Microfiche are \$3.00 each. Outside the United States and Canada, postage is \$3.00 for a photocopy or \$1.00 for a fiche.

ferent from 1.00 (*t* test). In 12 studies, it was less than 1.00, and in 19 studies, greater than 1.00 ( $P > 0.05$ , sign test). However, for individual neonates, one factor, generally  $L(V_D/V_T)$ , may assume predominance.

### Discussion

The minute ventilation requirements of infants who need mechanical ventilation cannot be predicted from their weights. The average requirement of 325 ml/kg/min for  $\dot{V}_N$  found for our patients is far larger than the normal requirement, and the range is so large that use of any "average predicted" figure would often result in severe hypoventilation. Similar results have been reported for adults in respiratory failure.<sup>13</sup>

This in no way detracts from the utility of measuring and monitoring minute ventilation in infants during mechanical ventilation. For a given infant during stable clinical conditions, the ventilatory requirement is often remarkably constant over 12 to 24 hours, and thus arterial blood  $P_{CO_2}$  may be kept reasonably constant simply by maintaining a constant minute ventilation. Moreover, a decrease of ventilatory requirements to near-normal levels (or a reduction of  $V_D/V_T$ ) can be a valuable objective sign of clinical improvement. A lower ventilatory requirement implies less work of breathing and the increased probability that the infant may be capable of sustaining the effort of breathing without mechanical assistance. If findings obtained from studies of adults can be extrapolated to infants,  $V_D/V_T$  may be remarkably constant in the face of moderate changes in tidal volume.<sup>14</sup>

The increased ventilatory requirement may have as its source either an increase in the load on the system (increased  $\dot{V}_{CO_2}$ ) or an increase in the inefficiency of the system (increased  $V_D/V_T$ ). We have shown that both these factors may be operative in our infants. Although the ventilatory requirement is directly proportional to  $\dot{V}_{CO_2}$ , it is a more complex function of  $V_D/V_T$ . However, it is proportional to the two normalized functions,  $L(CO_2)$  and  $L(V_D/V_T)$ , that we have derived. Using this approach, we have shown that an increase in either  $V_D/V_T$  or  $\dot{V}_{CO_2}$  may cause the increased ventilatory requirement of neonates. However, extreme increases in  $\dot{V}_N$  are more closely related to the increase in  $V_D/V_T$ . Thus, in five studies (fig. 2),  $L(V_D/V_T)$  was greater than 2.0.  $L(CO_2)$  never exceeded 1.89. However, on occasion, the metabolic load was sufficiently increased to be of possible significance from the standpoint of respiratory failure. In eight studies  $L(CO_2)$  was greater than 1.50. There was no relation between the increased ventilatory load due to metabolic factors,  $L(CO_2)$ , and that due to the inefficiency of ventilation,  $L(V_D/V_T)$ . Thus, from a

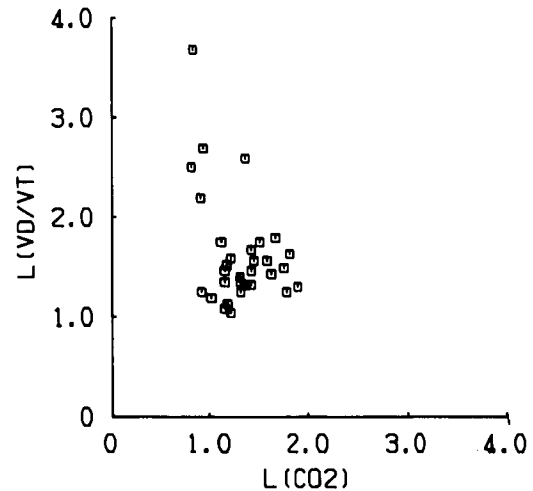


FIG. 2. Scattergram of the derived dimensionless parameters for the individual studies representing the pulmonary load,  $L(V_D/V_T)$ , and the metabolic load,  $L(CO_2)$ .

standpoint of ventilator design, provision of sufficient volume capacity for dealing simultaneously with the extreme ventilatory load that would occur from large increases in both  $L(V_D/V_T)$  and  $L(CO_2)$  would seldom be needed.

The absence of extreme elevations of  $\dot{V}_{CO_2}$  in our study population may be related to the disease processes common in neonates. Respiratory failure in neonates is usually cardiorespiratory failure, while in adult patients in a surgically oriented intensive care unit, respiratory failure is often but a small part of multisystem failure, accompanied by greatly increased metabolic loads.<sup>15,16</sup> It is therefore reasonable that inefficiency of ventilation is the hallmark of severe neonatal respiratory failure. Moreover, 70 per cent of our studies were done during mechanical ventilation. Thus, the metabolic load contribution resulting from increased work of breathing was minimized. During spontaneous breathing or during intermittent mandatory ventilation at very low rates, this may not be the case, and there may be a significant additional metabolic load component. For example, four of five spontaneously breathing older infants with bronchiolitis, reported by Downes *et al.*,<sup>17</sup> had large increases in  $\dot{V}_{CO_2}$ . In fact, when their published data are recalculated using our methods to determine  $L(CO_2)$  and  $L(V_D/V_T)$ , it is apparent that three of their patients had higher  $L(CO_2)$ s (range = 2.11–2.80) than any of the patients we report here. Such an increased  $CO_2$  production can no doubt aggravate respiratory failure.

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