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THE RESPONSIVENESS OF THE RESPIRATORY CENTERS IN CARDIACS WITH MITRAL VALVULAR DISEASE

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In testing the responsiveness of any neurological motor center the increase in the state of activation by a given increase of its specific stimulus has to be determined. For the respiratory centers, the gas tension of carbon dioxide in the arterial blood ($PaCO_2$) is considered to be the predominant stimulus. The best indication of the state of activation appears to be the total ventilatory volume per unit time.[17] A given increase of the arterial CO_2 pressure should lead to a specific increase in total ventilation, according to the following stimulus — response relationship: $\frac{\triangle \dot{V}}{\triangle PaCO_2}$.

If ventilation is measured in liters per minute and gas tension in millimeters of mercury, the thus obtained value will be the increase of ventilation in liters per minute effected by 1 millimeter of mercury increase in CO_2 tension. Henceforth, we will refer to this ratio as the quotient of responsiveness (QR).

The increase of the arterial CO_2 tension can be effected stepwise by inhalation of various concentrations of CO_2, or by the addition of artificial respiratory dead space. For our purpose, the most satisfying method seems to be a gradual increase in CO_2, brought about by a closed system of ventilation using no device for CO_2 removal. Such a method, somewhat modified from the one described by Julich[6] has been used in this experiment.

In this procedure, the subject inhales from an 80-100 liter reservoir of oxygen, to which the exhaled gas is returned (Fig. 1). The CO_2 of the circulating gas, therefore, gradually increases. Ventilation is measured by readings from a gasometer. Oxygen

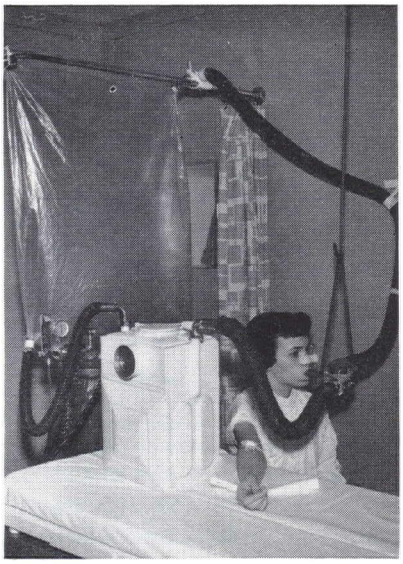

Fig. 1. Apparatus for testing respiratory response to variation in CO_2 concentration.

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is used instead of room air to ensure full arterial oxygen saturation throughout the test, therefore eliminating possible activation of the chemoreceptors for lack of oxygen. It also has the advantage of making the experiment better tolerated especially by cardiac patients for whom the desired levels of hyperventilation constitute considerable exertion. Through an indwelling Cournand needle in the brachial artery blood specimens are obtained in heparinized syringes at specific stages of the test. These are examined for O_2 and CO_2 content with the Van Slyke apparatus and technique, and for pH using a Cambridge electron-ray meter. Before the actual rebreathing study begins, the subjects breathe 100% oxygen usually for 25-30 minutes through the apparatus as described, until a steady state of ventilation and arterial CO_2 tension is reached.[7,16] The first sample of blood is drawn at this point. Subsequent samples are drawn at three levels of CO_2 increase in the inspired gas, as determined by concurrent ventilation measurements. Minute volume is calculated from three minute gasometer readings of the inspiratory volume immediately preceding the collection of each blood sample.

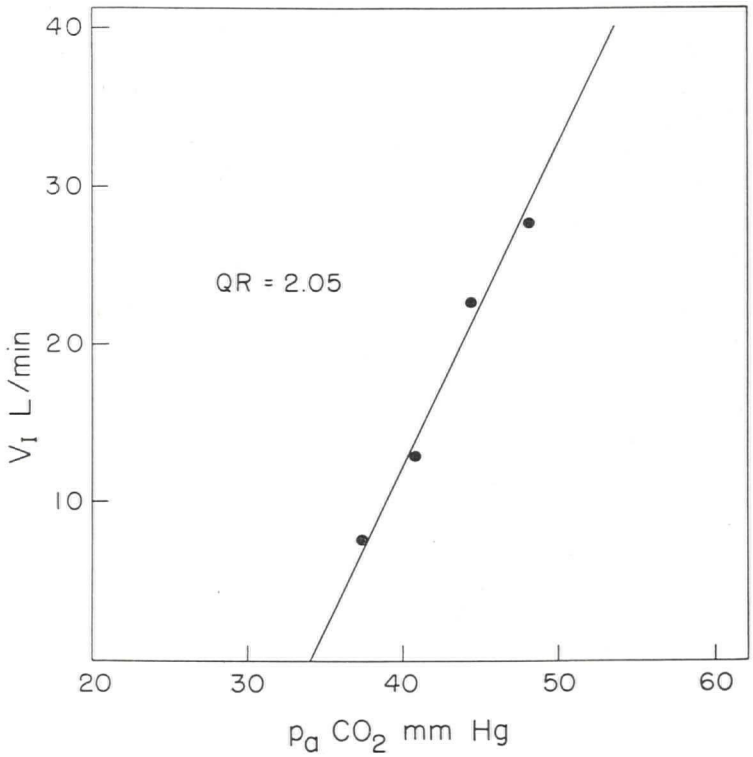

Fig. 2. Curve of respiratory minute volume from a normal person exposed to rising concentration of CO_2.

Fig. 2 represents the curve obtained by this method from a normal, 30 year old male. The relationship between $\dot{V}$ and $PaCO_2$ is a linear one.[1,5] This has been confirmed by our results. The time required to produce a minute volume of about three times the resting level (25-30 L/min.), was generally between 40 and 60 minutes. There is, of course, at no point a complete "steady state". Considering the slowness of CO_2 accumulation and the strictly comparative value of the obtained results, this

does not seem to be necessary. Gas samples obtained in eight tests at the end of the experiment from the inspiratory side of the circuit were analyzed using the Scholander technique. The CO_2 content was between 4.91% and 7.54%.

It is apparent that an increase of the CO_2 tension by 1 millimeter will produce a different respiratory response depending on body size and build. The obtained QR was therefore calculated per square meter body surface.

One of the main purposes of this study has been to establish a satisfactory and simple method. The most extensive knowledge of respiratory responsiveness using comparative methods has previously been acquired in pulmonary emphysema. Relatively little is known of respiratory responsiveness in cardiac patients. We have, therefore, studied a group of cardiac patients, mostly with valvular lesions amenable to surgery. Technically satisfactory results have been obtained thus far in 30 tests on 26 persons. Eight patients had rheumatic heart disease with either pure or predominant mitral stenosis (group I). These were subdivided as follows:

(a) two patients with less than 10 years duration since the active phase of rheumatic fever, functional classification I and II.

(b) six patients with more than 10 years duration since the active phase of rheumatic fever; their functional classification was II and III.

Fig. 3 represents the curve obtained from a 51 year old female with inactive rheumatic heart disease and a predominantly stenotic mitral lesion, who was known to have specific cardiac symptoms since the age of 31. The next group (group II)

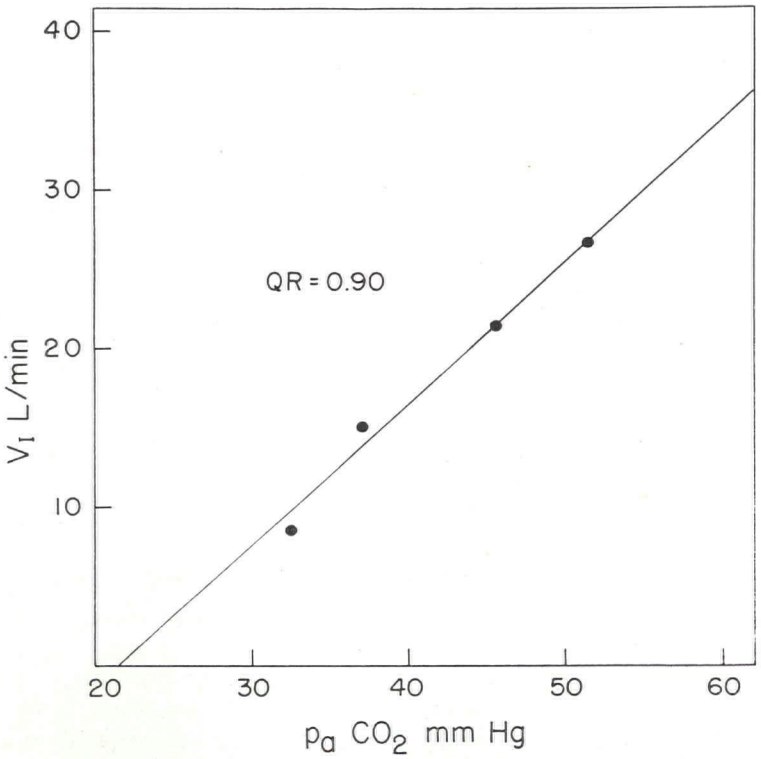

Fig. 3. Curve of respiratory minute volume from a patient with inactive mitral stenosis exposed to rising CO_2.

includes four patients suffering from rheumatic heart disease with combined mitral and aortic lesions, also belonging to the II and III functional classifications. The specific diagnosis in these two groups was made by clinical, X-ray and EKG findings, with the addition of left heart catheterization in some. A third group includes three patients with congenital heart disease, diagnosed as patent ductus arteriosus in two and interventricular septal defect in the third, confirmed by right heart catheterization. Functional classification in this group ranged from I to III. None of the patients was cyanotic. Two had marked pulmonary hypertension, while one had a normal pulmonary artery pressure.

The results which are essential for this study are averaged for the four groups and shown in Table I. Three tests on three patients with the diagnoses of idiopathic pulmonary fibrosis, arteriosclerotic heart disease with congestive heart failure and rheumatic mitral stenosis, complicated by severe anemia are not included. Seven patients in group I, all in group II and one in group III underwent corrective cardiac surgery. Only three patients have been studied post-operatively to date.

Thus far, we have been unable to demonstrate any significant deviation from the normal level in the groups with combined valvular lesions and congenital lesions. This might be due to the statistically insignificant number of patients examined. The average of a QR/m^2 of O.65 in patients with mitral lesions as compared to 1.03 in normals suggests a reduced responsiveness in the first group. These changes appear to develop late in the course of rheumatic heart disease.

DISCUSSION

The ventilatory response to the CO_2 stimulus has been studied by several authors,[1-14] with different methods of artifical CO_2 accumulation. Chronic diffuse pulmonary emphysema has been the main pathological entity investigated and shown to be associated with a decrease of the responsiveness of the respiratory centers. It has been questioned if this represents a true reduction in the central responsiveness.[2] The degree of activation of the centers can only be estimated indirectly through its effect upon the respiratory apparatus, which indeed, is grossly altered in pulmonary emphysema. While there is no doubt about the role of the mechanics of breathing in bringing about these changes, a true central alteration appears to be proven by several facts. The same decrease in responsiveness of the respiratory centers that occurs in pulmonary emphysema has been produced artificially in normal individuals by long term exposure to a CO_2 enriched atmosphere, without changes in the mechanics of breathing.[12] Conversely, respiratory responsiveness in two emphysematous patients seems to have been restored towards normal by long term treatment with artificial respiration, poducing marked diminution of the chronic CO_2 accumulation.[15] These findings, plus the fact that normal central responsiveness has been found in emphysematous patients without chronic CO_2 accumulation,[1] indicate the important role of chronic CO_2 overload in these central changes. Furthermore, responsiveness of the respiratory centers in normal subjects and emphysematous patients can be significantly altered by several drugs, such as morphine,[5] and salicylates, [13,14] and mecodin.[10]

Cyanotic congenital heart disease, chronic metabolic acidosis and alkalosis have been studied to a lesser extent in a comparable way. In these three conditions only chronic metabolic alkalosis was associated with a diminished responsiveness of the respiratory centers, which stresses again the role of CO_2 accumulation as the main factor.[1]

TABLE I

	No. of Pts.	Average Age	Average Resting Ventilation Under 100% O_2 per m^2 Body Surface	Arterial blood studies						
				Average Resting Arterial CO_2 Tension		Average Quotient of Responsiveness		Average pH	Average Oxygen Saturation	
				PCO_2					SO_2	
			V1 L/min./m^2	Under Room Air	Under 100% O_2	QR	QR/m^2	pH	Under Room Air	Under 100% O_2
GROUP I										
Rheumatic Heart Disease Pure Mitral Lesions										
Less than 10 yrs. duration since rheumatic fever	2	20	5.36	34.6	35.0	1.93	1.24	7.40	96.6	100
More than 10 yrs. duration since rheumatic fever	6	45	5.06	36.9	36.5	1.03	0.65	7.42	95.5	100
GROUP II										
Rheumatic Heart Disease combined Mitral and Aortic Lesions	4	42	6.16	35.0	34.5	1.49	0.95	7.42	97.1	100
GROUP III										
Congenital Heart Disease	3	32	5.29	36.0	34.4	1.69	0.99	7.41	88.7	100
NORMALS	8	34	4.67	37.8	38.3	1.85	1.03	7.42	96.7	100

Julich[5,11] has studied cardiac patients with a rebreathing method similar to the one used by us. He found an increased responsiveness of the respiratory centers in the over-all group with valvular lesions. In subdividing these patients according to their specific cardiac lesion, he found the values in patients with selective mitral lesions to be low normal or even diminished. We became interested in this fact as a possibility of obtaining more insight into the mechanisms of dyspnea in cardiacs with mitral lesions, which up to this time have not been fully explained by ventilatory and circulatory studies. The method might also have a certain value in estimating an unknown factor of secondary pulmonary disease in such patients.

Our results confirm to a more than expected degree the diminished respiratory responsiveness in patients with mitral valvular disease. The characteristic hyperventilation with hypocapnia found in other types of cardiacs is reduced in these patients, while their respiratory response to CO_2 accumulation resembles the one encountered in pulmonary emphysema. As indicated by the PCO_2 and pH values, there is no evidence of CO_2 accumulation in these patients. If these findings can be substantiated with a larger number of tests, we have here a pathological entity where diminished responsiveness of the respiratory centers cannot be explained by chronic CO_2 accumulation. Post-operative reexamination will give us an idea as to the reversibility of these changes.

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