STUDIES IN EXERCISE TOLERANCE AS AN AID TO CARDIOLOGICAL DIAGNOSIS AND ASSESSMENT

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A fuller understanding of the clinical physiology of human power and muscular activity has in recent years been made possible by several authoritative contributions.[1-11] These studies have made it logical and even imperative to try to understand the nature of the dynamic disruptions present in a state of limited functional capacity. Observations of various cardiopulmonary parameters reveal significant differences in achievement between healthy subjects, fit or unfit, on the one hand and physically limited patients on the other.[1,2,10,49]

Indices of physical fitness and performance based on such observations have found acceptance in the fields of military and industrial recruitment and research, and also in athletics.[2,12-19] The reliance placed on incorrectly comprehended parameters such as recovery pulse rates, or on ventilatory parameters, with failure to take cognizance of psychological factors, has made it difficult if not impossible to apply these indices to cardiopulmonary investigations.

A surer approach to the problems of exercise tolerance has been made possible by the application of the Fick principle, modified and adapted to the concept of a dynamic 'steady state' obtaining within a variable time after the commencement of physical exercise; and by the acceptance of A. V. Hill's theory that maximal oxygen consumption must be regarded as the ultimate measure of the estimation of oxygen consumption, which may exceed 30%. However, the measurement of pulmonary ventilation is very useful for investigating the maintenance of the steady state, since, when work that was originally 'steady state' work is continued, increase of pulmonary ventilation precedes and in many cases exceeds, the gain in oxygen consumption that is observed with approaching fatigue.[33]

After the initial exercise in the horizontal plane at constant speed, the gradient of the walking surface is altered to (say) 3°, and without interrupting the patient's stride a new exercise level is imposed and a new steady state assumed after an average of 5 minutes subject to the criteria enumerated above. Gas collection for the assessment of oxygen uptake is again carried out and, subject to the patient's subjective and objective reactions to the stressful situation, the next step-wise increase in work rate may be proceeded with, or alternatively a rest pause may be permitted. In the latter event the criteria for fresh 'steady state' attainment must once again be rigidly applied; it must, however, be remembered that the working interval before optimal oxygen uptake is achieved, grows commensurately shorter with increasing work grades.[35]

Maximal levels of oxygen uptake were not attempted in cardiac subjects and exercise was suspended if the patient requested it or upon the first clear objective indication of distress.

ECG recordings were obtained through the use of metallic screen electrodes, the placement of which corresponds for practical purposes to a unipolar lead V 3 - 4 and avoids as far as possible electromyographical interference. The graphs are of a fair technical standard and provide an accurate record of heart rate and disorders of rhythm.

Gas was collected in silicone-coated 50-ml. all-glass syringes and was withdrawn either from the spirometer bell (after the dead-space had been flushed 3 times with 'steady state' expired gas) or directly from the distal chamber of the expiratory valve. Parallel determinations have shown no significant discrepancies as a result of the varying mode of gas collection. Analysis of expired gas for oxygen uptake and carbon dioxide production was performed by the Haldane technique. Alternate samples were analysed in duplicate.

Maximal breathing capacities (MBC) were determined spirometrically over 15 - 20 seconds, the higher of two consecutive readings being taken as the relevant value, provided that the difference between the two readings was not of such magnitude as to render further determinations necessary.

Carbon-monoxide diffusion tests were performed at rest and during exercise in certain selected cases where the limitations of exercise tolerance was suspected to lie with that part of the oxygen transport system that is governed by pulmonary alveolar gaseous diffusion (the interplay of such factors as local over-ventilation and under-perfusion, or *vice versa,* on the one hand, and variable pulmonary capillary flow on the other, being responsible for an enhanced gradient of alveolar arterial oxygen).

Systemic arterial blood pressures as well as pulse pressures were measured by means of simultaneous tracings on the direct-writing recorder produced by an electronic oscillometer and a strain-gauge transduced from transmitted pulsations in the radial or princeps pollicis arteries of the right hand.

RESULTS

The following is a presentation of the findings in the subjects representative of the clinical groups specified above. In each case, and for each individual work level, energy expenditure has been predicted from given values for body weight, treadmill gradient, and speed. Assuming a 'true' metabolic respiratory-quotient value of 0·75 for working conditions, which is regarded as being the closest approximation,[38,39] the relevant caloric value of oxygen has been used to allow comparison with actually determined oxygen-uptake (Vo_2) levels. The latter have been expressed as a percentage of the predicted value.

According to Bobbert, treadmill energy expenditure may be predicted from the formula: $\text{Log } E_w = 1{\cdot}4272 + (0{\cdot}004591 \cdot v) + (0{\cdot}024487 \cdot \alpha + (0{\cdot}002658 \cdot v \cdot \alpha)$, where v = speed in metres/min. and α = gradient in degrees. Results are expressed in cal./kg./min. as stated above.

In the present series working conditions have been maintained within the limits implicit in the use of the formula, except that not all the patients were young men. In regard to sex, some workers have found lower levels for energy expenditure (E_w) in women performing treadmill exercise,[40] but others have denied this.[41] There seems to be fairly general agreement that E_w has higher values in older men than in younger men performing the same experiment.[42-44] Taking this into account, it seems reasonable to accept a wider application of the formula in providing reference values of 'normality' as a basis for comparison.

The actual predictions and measurements on normal persons (2), patients with mitral valve lesions (2), atrial septal defect (2), and cryptogenic cardiomyopathies (2), are set out in Tables I—IV.

DISCUSSION

1. *The Normal Group*

This includes two European males, R.C., aged 21, and G.D., aged 51, clinically free from any cardiorespiratory abnormalities (Table I). R.C. performed increasing grades of work up to his aerobic capacity; G.D., unwilling to exert himself maximally, performed only submaximal exercise.

Subject R.C. (Table I) consistently averaged an oxygen uptake of 128% of the predicted value. This was so at all work levels excepting the ultimate one. The first four grades also produced step-like increases in heart rate and minute ventilation which were found to bear a linear

TABLE I. NORMAL SUBJECTS

Subject	*Work rate (E_w) cal./kg./min.*	*Oxygen uptake ml./min. B.T.P.S.*	*Percent predicted E_w or Vo_2*	*Mean heart rate/min.*	*Ventilation l./min. B.T.P.S.*	*Respiratory frequency*	*Oxygen pulse ml./min.*	*Cardiac output l./min.*	*% Oxygen extracted*	*Respiratory quotient*	*Maxima. breathing capacity l./min.*	*Blood pressure (mm.Hg)*	*Pulse pressure (mm. Hg)*
R.C. (Eur. male) 21 yrs. 64·1 kg. 178 cm.	92·10 *(1,246)	†(112·36) 1,520	122·0	113	31·2	36	13·45	15·2	4·87	1·07	178·9		
	135·2 (1,829)	(189·22) 2,559	140·0	143	50·2	43	17·90	21·3	5·10	1·05			
	198·6 (2,686)	(235·44) 3,185	118·5	160	76·4	54	19·91	22·8	4·17	—			
	291·5 (3,943)	(379·9) 5,139	130·3	180	109·1	46	28·55	34·3	4·71	1·04			
	427·9 (5,788)	(275·37) 3,725	64·4	171	65·5	66	21·78	24·8	5·69	—			
G.D. (Eur. male) 51 yrs. 73·0 kg. 175 cm.	54·30 (836)	(94·7) 1,459	174·4	118	21·9	22	12·37	14·6	6·66	0·93		120/60	60
	72·73 (1,120)	(103·46) 1,595	142·3	120	27·4	27	13·29	16·0	5·82	1·02		160/80	80
	97·38 (1,500)	(113·98) 1,754	117·0	125	38·3	32	14·03	16·7	4·58	1·05		160/65	95
	130·5 (2,010)	(162·54) (2,504)	124·6	137	49·3	30	18·28	20·9	5·08	1·06		160/60	100

* Equivalent oxygen uptake for calorie requirement of external work. † Caloric equivalent of oxygen uptake.

capacity of the systems of oxygen transport and utilization governing aerobic muscular activity.[9,20,21]

Since in a steady state the amount of oxygen taken up by the lungs exactly equals the amount utilized by the tissues, minute by minute, then oxygen consumption and (where intra-individual equilibria and efficiency ratios remain constant) work rate also may be expressed in terms of the product of heart rate, stroke volume, and arteriovenous oxygen gradient. The interplay of these variables at differing rates of oxygen uptake has been the subject of valuable studies by Asmussen and Nielsen.[22,23] These workers used the techniques of inert-gas inhalation and dye dilution in the measurement of cardiac output in the dynamic state, repeated catheterization procedures for this purpose being impracticable. Investigations by Rushmer,[24] Chapman *et al.*,[25] Wyndham,[26,27] and others,[28,29] have provided further information on the interrelation of these circulatory parameters — their expected rate of change during various phases of aerobic work performance and their respective contributions to the final common product, viz. oxygen consumption or aerobic work potential. Since these parameters are in fact the denominators of all the other respiratory and circulatory factors and are determined by them, different patterns of response may be expected in various states of effort intolerance.

We have started work on techniques for the testing of exercise tolerance adapted to form an integral part of a clinical cardiological unit. In graded treadmill exercise we have aimed at maximum objectivity combined with simplicity of performance and a wide margin of safety, even in a severely incapacitated patient. These studies are intended to make available to the physician more precise information regarding the nature, extent and possible therapeutic implications of the patient's functional deficiency.

Predictions of energy expenditure exacted by varying work grades were made by Bobbert's formula, which expresses work energy (in cal./kg./min.) as a logarithmic function of gradient and speed of locomotion.[30,31] Actual oxygen uptake at comparable work levels, expressed as its calorie value at the relative respiratory quotient, and converted into cal./kg./min., may thus be compared with the predicted average normal requirements obtained from the formula.

MATERIAL, CONDITIONS AND METHODS

Effort studies and observations made at not less than four graded submaximal levels of work were carried out on cardiac patients in the three main categories: viz. those with valvular lesions, those with intracardiac shunts, and those with myocardial deficiencies (other than proved or suspected cases of coronary insufficiency with myocardial ischaemia). Assessments of maximal oxygen uptake and maximum heart rate were also attempted in a parallel series of normal controls, and sample findings will be presented without any attempt at a statistical formulation of the results at this stage.

All submaximal studies were made by subjects exercising on a motor-driven treadmill. The ergometer in use has a smooth, non-slippery rubber belt as walking surface and was driven at selected speeds varying between 3 and 7 km. per hour (50 - 117 metres per minute) and gradients between 0° and 12° with the horizontal. These conditions were chosen for a number of reasons: (1) They ensure a wide applicability in patients of varying age and ability, since they fall within the limits of everyday energy requirements and skills. (2) It has been determined that no significant contribution to energy production is afforded by the treadmill motor itself at speeds within the range specified.[32] (3) It has been found by several authors that the majority of subjects break their stride and start running at speeds of over 120 metres per minute.[9,31] (4) Bobbert's formula for energy expenditure is stated to be applicable only within this range of speeds and gradients. (5) The selection beforehand of a fixed working speed of 3 - 5 km./hour in cardiac patients and 7 km./hour in normal subjects allows progressive increases in gradient up to 12°, producing a satisfactory range of values for oxygen uptake without substantially altering the efficiency of work production. Simonson[33] has shown that for a range of walking grades between 3° and 6° there is at varying speeds a widely differing efficiency in the performance of external work. The highest efficiency is attained in normal subjects at medium speeds (about 4·8 – 5·6 km./hour) irrespective of gradient. It has been established also that a change of gait from walking to running at the same speed may actually reduce the rate of oxygen consumption in some cases.[31]

Furthermore, treadmill exercise has been shown to produce the highest oxygen consumption, especially on gradients; the maximal oxygen uptake is about 5% higher than in bicycle ergometry, skiing, or even in armwork while cycling.[34,35] This would seem to indicate that the largest effective muscle mass is operative during grade exercise and that this will induce correspondingly greater maximal oxygen uptake within the limits of adaptability of the oxygen transfer functions.[9,34]

Careful consideration was given to the attainment and maintenance of a dynamic 'steady state' during exercise testing, and to criteria reflecting it. A disregard of this principle may lead to unwarranted assumptions based on unrepresentative parameter readings (such as an 'unnecessarily' high ventilation rate for a particular grade of exercise). A 10-minute 'warming-up' period was allowed in all cases. Wherever possible, this was preceded by a conditioning session during which the subject was introduced to the special conditions of the test, and was familiarized with the technique of treadmill locomotion and with that of breathing through a mouthpiece with an expiratory valve. Resting conditions of heart rate, minute ventilation, respiratory frequency and oxygen uptake were recorded in the standing position once the patient had grown accustomed to spirometric technique. The 'warming-up' was performed on the horizontal with increments in the exercising speed until the previously selected test speed was attained. This varied between 3 and 7 km./hour, according to the subject's exercise status as gauged by the New York Heart Association's classification.[36] If after 10 minutes' constant exercise, the minute volume of ventilation and the heart rate agreed closely on two consecutive graphic recordings, a dynamic steady state was assumed to have been reached and the various respiratory and cardiovascular parameters, including oxygen uptake, were recorded at the end of a further 3 minutes' uninterrupted exercise. Expired air, collected in open circuit *via* a non-return respiratory valve (capable of transmitting high rates of flow at low frictional resistance) and 50-mm. corrugated rubber tubing, accumulates in a balanced Tissot-type spirometer of 170-l. capacity electronically calibrated in litres. Efficient gas mixing within the spirometer bell is promoted by twin centrifugal pumps. The nature of the direct-writing recording system makes possible a timed graphic representation not only of the electrocardiogram (ECG) but also of ventilation and respiratory frequency. 'Sampling' at any stage of the exercise test, including concomitant gas collections, may thus be accomplished with facility and accuracy. This is of paramount importance in monitoring the attainment and maintenance of the steady state as already explained. Implicit in the usage of parameters other than the 'final common pathway' of oxygen consumption (which cannot unfortunately be monitored during testing without the employment of electronic gas analysis) is the now well-established thesis that heart rate bears a linear relationship to oxygen uptake at all levels of aerobic muscular work up to work grades approaching the maximum.[1,2,10,11] Work by Ford and Hellerstein.[37] Simonson[33] and others has shown that there is a high correlation rate between estimated energy expenditure (cal./min.) or oxygen intake and pulmonary ventilation in normal subjects, but that a widely varying respiratory quotient and other factors in cardiac patients introduce an error in the relation to oxygen uptake, in accordance with the findings of many workers.[1,2,10,11,33,37]

The probable maximum oxygen-uptake value of 5·14 l./min. was determined at a level of work that also produced a maximal heart rate of 180 beats/min. and a peak minute ventilation of 109·1 l. or 61% of the maximal breathing capacity. The maintenance of a fairly constant oxygen-extraction percentage measured from expired-air analysis indicates that ventilation did not 'outstrip' the oxygen-uptake increment during the first four work grades. This suggests that, even at the work level that occasioned a 5·15 l. oxygen uptake, the aerobic requirements of working muscles were met under 'steady state' conditions. A constant heart rate of 180 beats per minute throughout this exercise grade supports this thesis.

The final work grade represents exercise at 7 km./hour on a 12° grade. The predicted metabolic cost of such work production (428 cal./kg./min. or 5·79 l. oxygen consumption) might well be expected to outstrip the subject's aerobic work potential and, although he was able to persevere for a period of 2 minutes, it is clear that a steady state was not attained. The oxygen uptake actually declined to a value representing about 50% of that which might have been expected. No further increase in heart rate had been possible; in fact, a submaximal value was shown. Ventilation had clearly become inefficient. At a respiratory frequency of 66/min., a minute volume of only 65·5 l. could be effected. This reflects the observation of Nielsen[45] that the physiological cost of ventilatory effort during maximal effort may exceed 9% of the total energy expenditure and place a prohibitive demand on the respiratory muscles in terms of oxygen requirement, and equilibrium can no longer be maintained. The fact that purely mechanical factors have not limited ventilatory increase is illustrated by the substantial 'reserve' in terms of maximal breathing capacity.

In considering the haemodynamics of this subject (and all the others) under working conditions, theoretical values for arteriovenous (A-V) oxygen differences have been used in calculating cardiac output, which with the A-V oxygen gradient jointly determines increases in oxygen uptake. The values substituted are based on the findings of Asmussen and Nielsen[22,23] and those of Wyndham[26,27] and others,[24,25] who showed A-V oxygen differences varying from 40·0 ml./l. at 0·25 l. oxygen uptake to a maximal value of 140 - 150 ml./l. at oxygen-uptake levels in excess of 3·0 l. The relationship is a polyphasic one, a sharp acceleration of rate of increase of A-V oxygen difference being noted at the 2·5 l. uptake level.

In R.C., both the cardiac output and the oxygen pulse, i.e. the gross oxygen intake divided by the corresponding heart rate, show an increase with increasing rates of work up to the maximal, paralleling the accelerated heart rate. The sustained rise in oxygen pulse demonstrates that even at the maximal heart rate of 180 per minute the blood circulation is fully effective in transporting oxygen in this man. The breakdown of the aerobic transport mechanisms at the final grade of work is underlined by the fall in cardiac minute volume and in oxygen pulse, which reflect a decline in stroke volume or A-V oxygen difference or both when the limitations of the 'steady state' equilibria have been exceeded. Though some 50% of the energy requirements at this final grade were quite obviously being met anaerobically, one final attempt at aerobic compensation is reflected in the sharp rise to 5·69% of the oxygen-extraction in the alveolar air.

The 'excessive' total oxygen consumption observed in R.C. in relation to predicted values might be regarded as purely fortuitous inasmuch as the formula is not intended for strict application to individual cases and a degree of scatter of normal values is to be expected, but it might also indicate the state of unfitness of this subject as compared with Bobbert's subjects, who were in training. It is well established that relatively higher oxygen-uptake and energy-expenditure levels are found in exercising subjects at the commencement of a training programme than those observed at comparable work grades after completion of the training. This presumably reflects a change in efficiency in the performance of muscular work.

The studies on subject G.D. (Table I) illustrate the response to physical exertion to be expected in the older individual. The findings are in accordance with those of Astrand for her older men,[44,46] except that G.D., unlike Astrand's truck drivers,[44] could not be considered well trained, though he was engaged in manual labour. He was also not highly motivated and could not be persuaded to attempt maximal effort.

The oxygen-uptake levels attained are far in excess of the predicted requirements. At the 2·5 l. uptake level, however, a value of 124·6% is obtained, representing a considerable decline in 'excessive' oxygen uptake when compared with the 174·4% of the lowest work level. If this ratio is to be considered as a measure of 'efficiency' in work production, as suggested above, then it seems reasonable to assume that aerobic muscular work is performed less efficiently in the older man. The steady decline in the predicted oxygen uptake with higher work levels, however, should not be interpreted as a sign of increasing efficiency, but rather as an indication of the rising contribution of anaerobic glycolysis to the metabolic energy requirements of enhanced working grades. This occurs despite the fact that the oxygen transport per pulse beat continues to rise. Minute ventilation shows normal increments and the respiratory frequency is not excessive; the alveolar oxygen-uptake ratio remains fairly constant. A 'fixed' heart rate at all levels was observed. All the abovementioned factors point to a preservation of dynamic 'steady state' conditions. The presence of an anaerobic contribution is however shown in the steady rise in the respiratory quotient; while R.C. at a heart rate of 113 could transport 1·52 l. of oxygen per minute (oxygen pulse 13·45 ml.), G.D. could transport at a heart rate of 118 only 1·46 l./min. (oxygen pulse 12·37 ml.). This finding suggests a slightly lower level of oxygen-carrying efficiency, but appears to be offset by the greatly enhanced oxygen pulse shown by G.D. at a heart rate of 137 beats per minute. This is accompanied by a substantial rise in cardiac output to which, it would seem, stroke volume and an increased pulse pressure have contributed to a greater extent than accelerated heart rate. Despite G.D.'s unwillingness to attempt near-maximal effort, it may be assumed that this level of 2·5 l./min. oxygen uptake represents about 70 - 80% of his aerobic work capacity. A likely maximal heart rate for this subject, according to Astrand's findings, would lie between 160 and 169 beats per minute.[46] Since only heart rate and A-V oxygen difference substantially contribute to oxygen uptake at levels above 2·5 l., it is seen that these factors, and more especially the heart rate, determine the lower aerobic capacity of the older man. While it is probable that efficiency of aerobic oxygen transfer in this man is maintained at levels near those for the younger subject by virtue of an enhanced stroke volume and/or A-V oxygen difference (the former is suggested by the rise in pulse pressure), such compensatory adjustments are not normally considered likely in the age group 50 - 60 years, and Astrand has found a very substantial decline in oxygen-pulse values with increasing age.[46]

2. *Mitral Valvular Lesions*

These constitute a very interesting group, and a rather characteristic pattern emerges from a study of the various exercise parameters at submaximal rates of work. This has been shown in catheterization studies undertaken by Donald *et al.*[47] and Gorlin *et al.*[48] in cases of rheumatic valvular disease. Both circulatory and ventilatory parameters may limit the aerobic work capacity of patients suffering from rheumatic heart disease, as Wyndham *et al.*[49] have demonstrated in their cardiac patients.

The subject R.K., European male aged 35 years (Table II), was placed clinically in Grade III for functional capacity (New York Heart Association[36]). He had atrial fibrillation. The clinical signs were those of severe mitral stenosis. He was, however, over-conscious of his heart condition, while the possibility of primary pulmonary disease could not be entirely excluded. However, good cooperation and a willingness to exert himself were encountered in this patient under test conditions. Exercise with a treadmill speed of 33 metres per minute (2 km./hour) was the most he was able to maintain for any length of time. Oxygen uptake and metabolic energy expenditure at the lowest level of work represented 184% of the predicted value, suggesting a gross inefficiency in oxygen utilization. The predicted oxygen uptake declined, however, to 88% with increasing work load, the *absolute* decrease in oxygen uptake indicating a marked breakdown of oxygen transfer mechanisms. (*Cf.* the *increase* in oxygen uptake that accompanies the declining percentage oxygen uptake predicted in the older normal subject G.D.) It is suggested that the heart rate of 130 beats per minute at the lowest level of work in R.K. is 'excessive' for this work grade, and explains in part the low oxygen-pulse value. Ventilation is not excessive and oxygen-extraction ratio in the alveolar air is within normal limits at this lowest work grade. A 'steady state' may reasonably be assumed to have been attained.

An increase in the work rate shows that the limits of aerobic functional capacity have been surpassed. The heart rate falls and there is a concomitant fall in estimated cardiac output (if a normal A-V oxygen difference is assumed for the particular level of oxygen consumption). A decline in the oxygen pulse is a further sign of inefficient oxygen transfer, indicating a fall in stroke volume and/or A-V oxygen difference. The reason for the moderate decline in minute ventilation is not clear; the effect is only partially compensated for by an increase in percentage oxygen uptake and a diminution of total oxygen uptake results. Mechanical factors are probably not limiting ventilation here, since a 'reserve' of nearly 75% is observed. This finding is in contrast to the hyperventilatory response that is occasioned by pulmonary congestion and oedema, where the loss of lung elasticity gives rise to subjective discomfort and results in dyspnoea. In R.K. there was no complaint of 'shortness of breath' as such.

A further increment in work load brings no substantial increase in heart rate. The minute ventilation does show moderate increase, but this is largely offset by a decline in the oxygen-extraction ratio. The oxygen pulse shows a further sharp decline, indicating that there has been yet another reduction in stroke volume or A-V oxygen gradient or both. The cardiac output falls still further. A steady state could not be assumed to have been attained in either of the higher work grades. Carbon monoxide diffusion tests yielded a fractional CO uptake of 81% under resting conditions, with a conductance (C_l) of 4·93 ml./min./mm.Hg. The former is somewhat high by normal standards,[50,51] suggesting enhanced pulmonary capillary perfusion. The low levels of conductance (including the slight increase to 5·97 ml. with mild exercise) may be ascribed to the relative hypoventilation. These findings would seem to indicate that R.K.'s poor ventilatory achievement might best be explained by the cost of ventilation in terms of oxygen consumption by the respiratory muscles. The low total oxygen uptake would be seriously encroached upon by even slightly increased ventilatory effort. A severe limitation of the cardiac output and its component factors is the decisive factor in limiting this patient's exercise tolerance.

The subject W.C., a Coloured female of 32 (Table II), with a predominant mitral incompetence, showed a similar pattern in respect of predicted and experimentally determined oxygen-uptake values, except that the actual values consistently fell short of predicted values. One may con-

TABLE II. MITRAL VALVULAR LESIONS

Subject	*Work rate (E_w) cal./kg./min.*	*Oxygen uptake ml./min. B.T.P.S.*	*Percent predicted E_w or Vo_2*	*Mean heart rate/min.*	*Ventilation l./min. B.T.P.S.*	*Respiratory frequency*	*Oxygen pulse ml./min.*	*Cardiac output l./min.*	*% Oxygen extracted*	*Respiratory quotient*	*Maximal breathing capacity l./min.*
R.K. (Eur. male), 35 yrs., 52·7 kg., 165 cm.	38·03 *(423)	†(69·87) 777	183·7	130	13·1	33	5·98	11·1	5·93	0·97	42·7
	47·88 (532)	(59·17) 658	123·6	125	10·8	32	5·26	10·1	6·09	0·98	
	60·29 (670)	(53·15) 591	88·2	130	13·5	37	4·55	9·8	4·38	1·08	
W.C. (Col. female), 32 yrs., 53·6 kg., 152 cm.	72·73 (823)	(49·43) 559	68·0	134	18·5	32	4·17	9·3	3·02	0·96	
	97·38 (1,101)	(35·72) 404	36·7	160	29·5	36	2·53	7·3	1·37	1·11	
	130·5 (1,476)	(13·70) 155	10·5	175	36·0	38	0·89	3·9	0·43	1·12	

* Equivalent oxygen uptake for calorie requirement of external work. † Caloric equivalent of oxygen uptake.

clude that in the presence of sharply declining oxygen-uptake rates, oxygen pulse, and cardiac output, there is a failure to establish a dynamic 'steady state' and that anaerobic mechanisms must play a dominant role in supplying energy requirements. This is further substantiated by the markedly non-linear relationship between minute ventilation and oxygen uptake. The heart rates are observed to be greatly in excess of normal values for work at comparable levels of oxygen uptake. This explains in part the extremely low oxygen pulse and, together with the diminished cardiac minute volume and oxygen uptake, implies a severe limitation of stroke volume. Breathlessness was the complaint that terminated effort testing in this subject, and it is possible that the highest minute ventilation rate attained seriously encroached on ventilatory 'reserve'.

Yet another subject, A.B., a European woman of 47, presented clinically with a severe degree of mitral stenosis and pulmonary hypertension. Catheterization studies revealed a fall in cardiac output from 5·376 l./min. under resting conditions with 0·293 l. oxygen consumption to 4·261 l./min. at an oxygen uptake of 0·407 l. The pulse rate showed a disproportionate rise to 110 beats per minute, but despite this finding the cardiac minute volume (as demonstrated by the direct Fick method) declined. This was effected by a drop in stroke volume from 67 ml. to 39 ml. Only a greatly enhanced oxygen-extraction ratio (9·55 vol. %) — the A-V oxygen gradient as determined by the method of Van Slyke and Neill[52] — was responsible for the measure of increase in oxygen uptake observed. These findings corroborate those recorded above in the other two subjects in this group, and serve to underline the fact that it is a sharp reduction in stroke volume rather than in the A-V oxygen gradient or any other factor that determines the low levels of oxygen pulse and cardiac output in patients with mitral valvular lesions. The frequent concurrence of atrial fibrillation provides an additional factor in reducing stroke volume.

3. *Cardiomyopathies of Uncertain Origin*

Both subjects in this category (Table III) were characterized clinically by cardiomegaly and recurrent cardiac failure of obscure origin. They complained of effort intolerance.

The subject R.J., European male aged 51 (Table III), showed an entirely normal response in the lowest work grade. An unequivocal steady state was reached, the heart rate was not 'excessive' and an oxygen pulse of 10·0 ml. was observed. Ventilation was within normal limits for this grade.

At the next work level a departure from the normal pattern was observed. A decrease in the oxygen pulse indicated a degree of inefficiency in oxygen transfer, and a non-linear increase in the minute ventilation was noted. A conspicuous feature was the steep rise in the respiratory quotient from 1·0 to 1·44, indicating a very substantial accumulation of 'excess lactate' and other products of anaerobic metabolism,[38,39] despite the fact that the oxygen uptake was maintained near to 'expected' levels. Inconstant bigeminy was detected by ECG. At a slightly higher work grade the previously observed oxygen-uptake level of 1·19 l. could no longer be maintained, despite a further rise in heart rate. Respiratory frequency and minute ventilation were now excessive, the latter reaching some 42% of the maximal breathing capacity. The respiratory quotient attained the value of 1·51, emphasizing the dominant role of anaerobic glycolysis in meeting energy requirements. A sensation of imminent syncope rather than of dyspnoea terminated the effort.

The subject J.R., a Coloured male of 36 (Table III), cooperated eagerly in performing exercise tests, and was thought to exaggerate his effort intolerance. His performance at the lowest work rate imposed showed a normal response except that voluntary hyperventilation occasioned a low alveolar oxygen-extraction ratio and an 'artificially' increased respiratory quotient. (A degree of hyperventilation with 'washing out' of carbon dioxide probably explains the rather high RQ levels observed in a number of other subjects at low work grades. This may be ascribed to unfamiliarity with mouthpiece-breathing techniques.) At the second level of exercise an entirely normal response was elicited. A further rise in oxygen pulse was observed at the third grade, and oxygen-uptake level is increased commensurately with estimated energy expenditure.

The following (fourth) work grade, however, brought a significant decline in the ratio of observed to expected oxygen uptake and this was paralleled by a fall in oxygen pulse from 14·0 to 12·9 ml. indicating a definite inefficiency in oxygen transfer. As the fault does not lie with an 'excessive' pulse rate it must be sought among stroke volume, A-V oxygen difference, and their contributory factors.

The final (near-maximal) work grade shows a further diminution in oxygen uptake relative to expected values and, though the oxygen pulse rises once more, this is

TABLE III. CRYPTOGENIC CARDIOMYOPATHIES

Subject	*Work rate (E_w) cal./kg./min.*	*Oxygen uptake ml./min. B.T.P.S.*	*Percent predicted E_w or V_{O_2}*	*Mean heart rate/min.*	*Ventilation l./min. B.T.P.S.*	*Respiratory frequency*	*Oxygen pulse ml./min.*	*Cardiac output l./min.*	*% Oxygen extracted*	*Respiratory quotient*	*Maximal breathing capacity l./min.*
R.J. (Eur. male), 51 yrs., 74·5 kg.,	54·30 *(854)	†(64·31) 1,011	118·4	101	25·4	28	10·01	12·6	3·98	1·01	150·6
174 cm.	72·73 (1,143)	(75·76) 1,191	104·2	120	38·2	28	9·93	13·2	3·12	1·44	
	97·38 (1,531)	(73·28) 1,152	75·3	128	63·3	36	9·00	12·8	1·82	1·51	
J.R. (Col. male), 38 yrs., 65·0 kg.	45·37 (622)	(70·26) 964	154·9	80	31·1	50	12·05	12·1	3·10	1·13	121·1
163 cm.	58·91 (808)	(80·61) 1,106	136·8	84	21·8	35	13·17	12·3	5·07	—	
	76·45 (1,049)	(94·17) 1,292	123·2	92	25·6	35	14·04	13·6	5·04	1·07	
	99·26 (1,362)	(100·36) 1,377	101·1	107	33·8	45	12·87	13·8	4·07	1·02	
	128·8 (1,767)	(127·84) 1,754	99·3	117	43·6	45	14·99	16·7	4·02	1·14	

* Equivalent oxygen uptake for calorie requirement of external work. † Caloric equivalent of oxygen uptake.

effected largely at the expense of heart rate, which does not rise commensurately. Ventilation cannot yet be regarded as excessive, but a respiratory quotient of 1·14 at the 1·75 l. oxygen-uptake level suggests approaching decompensation.

4. *Left-to-right Intracardiac Shunts*

Two young European female subjects, B.G. aged 22 and H.R. aged 23 (Table IV), were subjected to exercise tolerance studies. Both complained of mild breathlessness on moderate effort.

Subject B.G. (Table IV) experienced palpitations. At the lowest exercise level she exhibited an oxygen uptake representing slightly less than 50% of the predicted value for the particular grade of exercise. This is hard to explain since the minute ventilation is within normal limits; the oxygen-extraction percentage, however, is extremely low. The heart rate of 108 beats per minute may or may not be slightly excessive.

The three succeeding work levels exhibit an observed oxygen uptake which approximates very closely to the predicted value in each case. A steadily rising oxygen pulse reflects a satisfactory state of efficiency in oxygen transfer and indicates that the pulse-rate increments, though substantial, are not excessive. The maximal pulse rate recorded under the imposed experimental conditions was 188 beats per minute and this value must be very close to the true maximal heart rate. Allowing for the bias towards higher oxygen-uptake values at near-maximal heart rates due to the steep rise in the A-V oxygen gradient,[11] it would still appear that 1·95 l./min. would represent a fair approximation for the maximal oxygen uptake, and this must be regarded as slightly subnormal for a woman of this age. This is not an unexpected finding when it is remembered that the work of the heart is increased and that a higher pulse rate is necessary to achieve a systemic cardiac output equivalent to that attained where no shunt exists, all other factors being equal. Alternatively, stroke volume may be increased, and this would explain more nearly the observed increases in oxygen pulse. A substantial rise in pulse rate might be expected to have a contrary effect.

Subject H.R. (Table IV) exhibits similar features. There are some noteworthy differences, however. Excessive body weight naturally exacts a higher oxygen-uptake requirement for an equivalent rate of external work production, and also a higher heart rate; so that the limits of aerobic capacity (which is not proportionately increased) are attained and exceeded at relatively low levels of mechanical work. At the lowest work grade here imposed, a state of hyperventilation with tachypnoea, resulting in a raised RQ, is observed. At higher rates of work production it is seen that ventilation is adequate though not excessive, and oxygen uptake maintains a constant relationship to the predicted metabolic requirement. Oxygen pulse and cardiac output rise steadily. At the highest level imposed, however, there is evidence of approaching decompensation in respect of aerobic transfer mechanisms. This is expressed in a declining oxygen-uptake 'efficiency ratio' and a marked rise in respiratory quotient. Oxygen pulse and cardiac minute volume are still adequately maintained, use undoubtedly being made of an appreciable rise in pulse pressure which permits maintenance of cardiac output at a heart rate that is not excessive. The observed heart rate of 172/min. and the oxygen uptake of nearly 2·4 l. must be regarded as near-maximal, and are within normal limits.

The Valsalva manoeuvre failed to produce a decline in arterial oxygen saturation as determined by ear oximetry, indicating that the direction of flow of the intracardiac shunt could not be reversed by this means.

SUMMARY

1. The application of a prediction formula in assessments of the efficiency of aerobic supply mechanisms is discussed in relation to graded muscular work on a treadmill. The significance of a constant ratio of experimentally determined to predicted aerobic energy expenditure is evaluated as a measure of efficiency, and the possible meaning of a ratio 'fixed' in excess of 100% is considered. A conclusive decline in this ratio with increasing levels of work was considered to parallel the rise in respiratory quotient in reflecting anaerobic contributions to energy expenditure. The assumption is made that efficiency of mechanical work production remains constant in the individual subject at any fixed treadmill speed, irrespective of changes in gradient.

2. The range of normal values for the various cardiorespiratory parameters involved in the maintenance of the dynamic 'steady state' and their interrelation are considered. The criteria for judging attainment, maintenance and exceeding of aerobic functional capacity are presented.

3. The contributory factors in the severe limitation of muscular-work capacity experienced by subjects suffering from mitral valvular disease are outlined; and the critical fall not only in oxygen uptake but also in oxygen pulse and cardiac output is shown to be due in great measure to a severely limited stroke volume. In severe cases the compensatory rise in heart rate and especially in tissue oxygen-extraction ratios is unable to meet the increasing aerobic requirements of muscular-

TABLE IV. ATRIAL SEPTAL DEFECTS

Subject	*Work rate (E_w) cal./kg./min.*	*Oxygen uptake ml./min. B.T.P.S.*	*Percent predicted E_w or V_{O_2}*	*Mean heart rate/min.*	*Ventilation l./min. B.T.P.S.*	*Respiratory frequency*	*Oxygen pulse ml./min.*	*Cardiac output l./min.*	*% Oxygen extracted*	*Respiratory quotient*	*Maximal breathing capacity l./min.*	*Blood pressure (mm.Hg)*	*Pulse pressure (mm. Hg)*
B.G. (Eur. female) 22 yrs. 53·2 kg. 164 cm.	64·54 *(725)	†(31·99) 359	49·6	108	19·4	27	3·32	7·2	1·85	0·95			
	89·06 (1,000)	(87·98) 988	98·8	132	32·0	33	7·48	12·3	3·09	—			
	122·9 (1,380)	(116·8) 1,312	95·0	172	52·9	40	7·63	13·8	2·48	0·96			
	169·6 (1,904)	(170·3) 1,913	100·5	188	61·1	38	10·18	17·4	3·13	—			
H.R. (Eur. female) 23 yrs. 80·0 kg. 165 cm.	54·30 (917)	(70·97) 1,198	130·7	123	30·5	50	9·74	13·3	3·92	1·13	93·8	175/90	85
	72·73 (1,228)	(98·39) 1,661	135·3	133	37·7	39	12·49	15·8	4·40	0·93		180/70	110
	97·38 (1,644)	(123·16) 2,079	126·5	158	52·4	47	13·16	18·9	3·97	1·12		220/110	110
	130·5 (2,203)	(141·8) 2,395	108·7	172	69·8	54	13·92	20·8	3·43	1·20		220/80	140

* Equivalent oxygen uptake for calorie requirement of external work. † Caloric equivalent of oxygen uptake.

work production. Ventilatory factors played a decidedly lesser role in limiting the exercise tolerance of these two subjects.

4. The heterogeneous group of the cardiomyopathies seems to be characterized by a critical level of oxygen transfer and utilization. Up to this level, aerobic requirements of muscular work production can be met in full; but, if this level is exceeded, a phase is entered upon where anaerobic glycolysis plays an increasing part. This may be due in part to the limitations set upon the cardiac output by a maximal heart rate that is lower than normal; but there is also evidence of inefficient oxygen utilization.

5. In one of the cases of atrial septal defect studied, an absolute limitation of maximal oxygen uptake was observed and pulse rates were regarded as excessive for the rate of work production. Only at the highest levels of energy expenditure, however, was there a clearly definable breakdown in aerobic supply mechanisms. In a second patient, the maximal oxygen-uptake level attained was within normal limits, but a significant contribution of anaerobic energy transfer suggested that here, too, there was some limitation of total aerobic functional capacity in accordance with the known overload imposed on the myocardium by the anatomical abnormality. All other parameters were within normal limits.

6. It is concluded that further studies in exercise tolerance in a variety of cardiac disabilities might establish definite trends of abnormal response, if careful analysis of the parameters involved in the pathogenesis were undertaken. The better understanding that ensued from an appreciation of the dynamic physiological derangement involved might well contribute to a more logical approach to the diagnosis, prognosis and therapy of the underlying cardiorespiratory abnormality that has manifested itself — non-specifically — in a diminished capacity for muscular effort.

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