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Gas Exchange during Exercise in Children with Thalassemia Major and Diamond-Blackfan Anemia

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ABSTRACT. The two main goals of this study were: 1) to determine how O_2 uptake, ventilation, and CO_2 production during exercise were acutely affected by transfusion in children with congenital anemia (thalassemia major and Diamond-Blackfan syndrome) requiring hypertransfusion and chelation therapy and 2) to compare gas exchange responses to exercise of the anemic patients to normal values. Thirteen patients (age range 7–27) performed cycle ergometry with a progressively increasing work rate. Gas exchange was measured breath-by-breath. Tests were done before and after routine transfusion (mean increase in hematocrit 22%). The results were compared to 10 age-matched normal children who performed the same protocol on two occasions separated by a 2-day interval, and to the results of 109 normal children studied in this laboratory. Transfusion resulted in: 1) a small, but significant increase in the anaerobic threshold (9%) and 2) an increase in the slope of the relationship between O_2 -uptake and heart rates. Despite these improvements, the majority of the patients had abnormally low values of maximal O_2 uptake, anaerobic threshold, and slope of the O_2 uptake-heart rate relationship. The abnormalities were more marked in the older patients. Measurement of gas exchange during exercise may be helpful in determining an optimal hematocrit for patients on hypertransfusion regimens. (*Pediatr Res* 19: 1215–1219, 1985)

Abbreviations

AT, anaerobic threshold
HR, heart rate
 V_E , ventilation
 $\dot{V}CO_2$, CO_2 output
 $\dot{V}O_2$, O_2 uptake
 $\dot{V}O_{2max}$, maximal O_2 uptake (peak $\dot{V}O_2$)
2,3-DPG, 2,3-diphosphoglycerate

In patients with severe anemia such as thalassemia major and congenital erythroid hypoplasia (Diamond-Blackfan syndrome), the goal of therapy is to maintain an "optimal" hematocrit (1–5). Ideally, this is a regimen in which frequency of transfusion is

sufficient for normal cardiovascular and respiratory function at the same time that the consequent iron overload can be eliminated by chelation therapy. In addition, the presence of heart and lung impairment—known to occur in many of these patients (6–8)—may alter cardiorespiratory function to the extent that the "optimal" hematocrit may vary from patient to patient.

We reasoned that measurement of gas exchange during exercise could prove useful in these patients since it allows an assessment of the response of the cardiovascular and respiratory systems to increases in metabolic demand. The measurement of the dynamic responses of $\dot{V}O_2$, V_E , and $\dot{V}CO_2$ (e.g. the anaerobic threshold) to exercise has not been frequently used to assess cardiac and respiratory function in children, but the ability of the organism to consume atmospheric O_2 is the final and critical product of adjustments of cardiac output and ventilation. Thus, the analysis of gas exchange during exercise yields an insight into the adequacy of a patient's response that cannot be obtained from measurements of cardiac output or ventilation alone.

The present study was designed with two goals: 1) to compare the gas exchange responses to exercise in children with congenital anemia to those in a large group of normal children previously studied in our laboratory (9, 10) and 2) to examine how the gas exchange responses in the patients were acutely affected by transfusions.

METHODS

Population. Thirteen patients, 11 with β -thalassemia major and two with Diamond-Blackfan syndrome, ranging in age from 7 to 27 yr comprised the sample population. Age, height, and weight for the individual subjects appear in Table 1. None of the patients had a history of heart failure or arrhythmia, nor were any on cardiac medications at the time of the study. In addition to the hypertransfusion regimen, all patients were receiving daily subcutaneous doses of desferoxamine via slow-rate constant infusion pumps. None of the patients had a history of respiratory disease. Informed consent was obtained from each subject and, where appropriate, parent or guardian.

Protocol. Exercise testing was done between 6 and 18 h before routine blood transfusion and between 18 and 36 h after transfusion (thereby ensuring a reequilibration of the intra and extra-vascular fluid volumes). The exercise protocol consisted of cycle ergometry. Following a 3- to 4-min period of unloaded pedalling, a continually increasing (10 W/min) work rate ("ramp"-pattern) was applied to the ergometer (11). The patients were told that they would feel as if they were going up a steep hill, and that they should continue pedalling for as long as they felt comfortable. This particular protocol was chosen because it allows the measurement of a number of important aerobic parameters of

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Table 1. Characteristics of 13 patients with congenital anemia with pre- and posttransfusion hematocrit and 2,3-DPG levels

Subject	Age (yr)	Wt (kg)	Ht (cm)	Hematocrit (pre) (%)	Hematocrit (post) (%)	2,3-DPG (pre) ($\mu\text{mol/gHb}$)	2,3-DPG (post) ($\mu\text{mol/gHb}$)
1	10.4	30.2	130	34	45	14.2	15.9
2*	10.4	38.2	144	33	41	13.7	15.1
3	11.6	36.8	144	31	42	11.9	18.2
4*	27.0	42.3	150	34	38	12.5	12.3
5	17.0	62.0	150	29	39	15.5	11.7
6	7.0	22.0	114	23	33	13.3	10.9
7*	13.1	32.0	137	32	40	12.5	16.8
8	10.8	43.9	143	32	35	14.2	12.7
9	17.1	69.0	170	27	38		
10*	15.0	37.3	138	34	43	15.0	12.0
11	13.8	44.0	156	33	34	14.5	12.4
12	10.7	29.0	127	36	39	13.8	12.5
13*	13.0	29.0	135	34	41	13.4	12.9
Mean $\pm$ SD	13.6 $\pm$ 5	39.7 $\pm$ 13	141.4 $\pm$ 14	32 $\pm$ 4	39 $\pm$ 4	13.7 $\pm$ 1.1	13.6 $\pm$ 2.3

* Females.

exercise in a single, brief test. Thus, long periods of exercise and the possibility of incurring a significant metabolic acidosis and prolonged fatigue were avoided.

A mass spectrometer was used for rapid analysis of O_2 , CO_2 , and N_2 concentration. Ventilation was measured either by a turbine volume transducer or by inspiratory and expiratory pneumotachographs and low resistance breathing valves. The electrical signals from these devices underwent analog-to-digital computation for the on-line, breath-by-breath determination of $\dot{V}\text{O}_2$ (STPD), $\dot{V}\text{CO}_2$ (STPD), $\dot{V}_E$ (BTPS); respiratory exchange ratio, ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}\text{O}_2$) and CO_2 ($\dot{V}_E/\dot{V}\text{CO}_2$), and end-tidal partial pressures of O_2 and CO_2 as previously described (12). The data from each test were displayed on-line and stored on digital tape for subsequent analysis. The breath-by-breath data of each subject were interpolated at 1-s intervals, and moving averages could be obtained for smoothing of studies with a great deal of breath-to-breath variation.

Parameters of Gas Exchange Measured. $\dot{V}\text{O}_{2\text{max}}$. This was the highest (or peak) $\dot{V}\text{O}_2$ achieved by the subject.

AT. The highest metabolic rate (work rate) for which the energy requirements may be obtained solely from O_2 uptake, and, hence, without concomitant anaerobiosis. This was determined from gas exchange data by finding the $\dot{V}\text{O}_2$ at which $\dot{V}_E/\dot{V}\text{O}_2$ increases without an increase in $\dot{V}_E/\dot{V}\text{CO}_2$ (hyperventilation with respect to O_2) (9, 11, 13).

Relationship between $\dot{V}\text{O}_2$ and HR. This was an index of the cardiac response to the increasing metabolic requirement of exercise (10). HR was measured beat-by-beat using three anterior chest leads and the EKG was in continuous view via a high persistence EKG oscilloscope. Linear regression techniques were used to obtain the slope of the relationship between $\dot{V}\text{O}_2$ and HR ($\Delta\dot{V}\text{O}_2/\Delta\text{HR}$) below the AT during the exercise protocol.

Pre- and posttransfusion venous blood samples were obtained immediately prior to exercise for measurement of Hb concentration by standard techniques. Levels of 2,3-DPG were measured using an enzymatic method (Sigma Corp.). These measurements are included in Table 1. The mean increase in Hb concentration was 22%.

Control Group. To test for any possible systematic effects on gas exchange related to the study design (*i.e.* exercise on day 1 followed by exercise 2 days later), 10 healthy children were used as normal controls (mean age 11.8 yr, range 7–16 yr). They, like the anemic patients, had no previous experience in our exercise laboratory. Cycle ergometry testing was performed on day 1, then repeated on day 3. Similar to the anemic patients, no attempt was made to actively encourage the normal subjects to continue exercising at the higher work rates.

Normal Predicted Values of Gas Exchange Parameters. These were obtained from a previous study in this laboratory in which cycle ergometry with ramp protocols was performed by 109 normal children ranging in age from 6 to 17 yr old (9, 10). For the one subject aged 27 yr, predicted values were obtained from studies done with adults in this laboratory (14). Predicted values were based on each patient's body weight and gender. We used weight rather than age since many patients with thalassemia major have small body sizes for their age compared to normals, therefore, predicted values based on age would bias the interpretation of the results.

An activities questionnaire designed in this laboratory to subjectively assess levels of physical activity at home and at school was administered to the patients. The results were compared to those obtained in 109 normal children.

The independent *t* test was used to compare the results of the patients to those of the normal controls. To determine if the hypertransfusion had an effect on cardiorespiratory variables, an analysis of paired differences was made using the dependent *t* test. Statistical significance was taken at the $p < 0.05$ level. Results are expressed as mean $\pm$ 1 SD. For illustration of certain gas exchange variables, pretransfusion values in all 13 patients were superimposed and averaged (group-mean response) and compared to the posttransfusion values. This analysis is used as a noise-reducing technique for this type of data (16).

RESULTS

The results of exercise testing in the 10 control subjects were all within the normal range of our laboratory. Prior to transfusion, the $\dot{V}\text{O}_{2\text{max}}$ values of the patients were significantly lower than normal (mean of $71 \pm 24\%$ predicted) (Figs. 1 and 2). Twelve of the 13 patients were below their predicted value and five were below 2 SD. (Consistent with this, the mean $\dot{V}\text{O}_{2\text{max}}$ of the patients was significantly lower than the mean $\dot{V}\text{O}_{2\text{max}}$ of the 10 control subjects.) There was no significant change in $\dot{V}\text{O}_{2\text{max}}$ in the patients following transfusion (mean pretransfusion $\dot{V}\text{O}_{2\text{max}}/\text{kg}$ was 28.6 ± 9.8 ml $\text{O}_2/\text{min}/\text{kg}$; posttransfusion was 30.2 ± 8.6 ml $\text{O}_2/\text{min}/\text{kg}$) nor was there any change in the normal controls from day 1 to day 3. In addition, the patients achieved a mean maximal respiratory exchange ratio of 1.15 prior to transfusion and 1.18 following transfusion.

In contrast to the $\dot{V}\text{O}_{2\text{max}}$, there was a small but significant increase in AT following transfusion. This occurred in 10 of 13 patients with a mean increase of $9 \pm 14\%$ while no change was observed in the control group (Fig. 3). An example of this increase in AT is shown in one of the patients in Figure 4. Although the

Fig. 1. $\dot{V}O_2$ max in patients (closed circles) before and after transfusion and in controls (open circles) on days 1 and 3. Results have been normalized to body weight. This value remains constant throughout childhood in normal subjects (9). The horizontal bars represent the mean values. There was no difference in $\dot{V}O_2$ max before and after transfusion in the patients or between the first and second visits in the normal controls.

Fig. 3. Anaerobic threshold in patients (closed circles) before and after transfusion and in normal controls (open circles) on days 1 and 3. Results have been normalized to body weight. This value remains constant throughout childhood in normal subjects (9). The horizontal bars represent the mean values. AT increased in the patients by a small but significant amount following transfusion. No difference was observed in the controls between days 1 and 3. In addition, AT in the patients was below normal in the majority of patients both before and after transfusion.

Fig. 2. Pretransfusion values of AT (top panel), $\dot{V}O_2$ max (middle panel), and slope of the $\dot{V}O_2$ -HR relationship (bottom panel) expressed as percentage of predicted as a function of age in the patients with anemia. The shaded area represents the mean $\pm$ 2 SD of normal values based on the subject's weight and gender. The mean predicted value for each parameter (100%) is shown as the dashed lines. The value of each of these exercise parameters decreased with increasing age. Best-fit line by least squares is shown with the solid lines. The mean correlation coefficient was -0.52 .

Fig. 4. Determination of the AT before (dashed lines) and after (solid lines) transfusion in a patient with thalassemia major. The noninvasive measurement of the AT involves finding the $\dot{V}O_2$ where $\dot{V}E$ increases out of proportion to $\dot{V}O_2$, but while the increase in $\dot{V}CO_2$ parallels that of $\dot{V}E$. This is shown as the point where $\dot{V}E/\dot{V}O_2$ increases without an increase in $\dot{V}E/\dot{V}CO_2$. As indicated by the arrows, the AT increased in this patient following transfusion.

increase in AT was greater in the patients aged 12 and younger (mean increase of 15%) compared to the seven older subjects (mean increase of 4%) those values did not differ significantly.

The mean AT of the patients prior to transfusion was significantly lower than predicted, $75 \pm 16\%$ (Fig. 2). All 13 patients were below their mean predicted and two were less than 2 SD of the normal. (Consistent with this, the mean AT of the patients was significantly lower than the mean AT of the 10 control subjects.) Despite the improvement after the transfusion, the mean AT of the anemic patients remained significantly lower than predicted ($84 \pm 20\%$) with 11 of the 13 patients remaining below their predicted value.

Nine of the 13 patients had slopes of the $\dot{V}O_2$ -HR relationship which were below predicted and three were less than 2 SD (Fig. 2). The slope of the $\dot{V}O_2$ -HR relationship increased significantly in the patients following transfusion (nine of 13 increased; mean of 16%). This is consistent with the group mean response of HR and $\dot{V}O_2$ shown in Figure 5 demonstrating a relative tachycardia prior to transfusion. The change in the slope of the $\dot{V}O_2$ -HR relationship in response to the transfusion was significantly greater in the six children aged 12 and younger (mean increase of 36%) compared to the seven older children (mean increase of 13%).

There was no significant change in the levels of 2,3-DPG following transfusion. The mean pretransfusion level was $13.7 \pm 1.06 \mu\text{mol/g Hb}$ compared to the posttransfusion level of 13.6 ± 2.3 . These values were all within the normal range of nonanemic patients established in this laboratory (10 – $16 \mu\text{mol/g Hb}$), but were considerably lower than expected for the degree of anemia. There was no correlation between the magnitude of the increase in AT and the change in levels of 2,3-DPG.

The activities questionnaire scores of the patients were indistinguishable from test values obtained in normal children. The patients' mean value was $105 \pm 32\%$ predicted of the activity of normal children as assessed by the questionnaire. No predicted value was available for the 27-yr-old patient.

DISCUSSION

$\dot{V}O_{2\text{max}}$ and AT were low in the patients as a group both before and after transfusion, and severely so in a number of them (Figs. 1–3). This indicates that O_2 availability is limited at lower than normal metabolic rates resulting in lactic acid production. Buffering of the lactic acid by HCO_3^- results in increased CO_2 production relative to $\dot{V}O_2$. The increase in $\dot{V}CO_2$ causes a rise in $\dot{V}_E$, and forms the basis for the noninvasive determination of the AT (Fig. 4).

There are several possible explanations for the low AT and $\dot{V}O_{2\text{max}}$. First, a reduction in arterial O_2 tension has been documented previously in patients with thalassemia major (7, 8). Apparently, this is consequent to pulmonary vascular disease

that develops in many of these patients (7, 16, 17). Second, the cardiomyopathy that often accompanies hemosiderosis may lead to a reduced cardiac output and insufficient O_2 delivery to the working muscle cells during exercise. In fact, left ventricular dysfunction has recently been documented in asymptomatic patients with thalassemia with the technique of exercise radio-nuclide angiography (18). Third, anemia itself reduces arterial O_2 content and this may affect O_2 transport at the cellular level. Consistent with this are preliminary studies in this laboratory showing that normal subjects made anemic by phlebotomy have reductions in the AT (19).

Caution must be used in interpreting $\dot{V}O_{2\text{max}}$ in patients because it is a highly effort-dependent parameter of aerobic exercise. A true $\dot{V}O_{2\text{max}}$ implies that a plateau of $\dot{V}O_2$ was achieved despite increasing work rate, but less than a third of normal children studied in this laboratory, who were actively encouraged to continue exercising at high work rates, actually achieved such a plateau (9). In the present study, neither the patients nor the control subjects were actively encouraged at higher work rates, and only one patient achieved a true plateau. Nonetheless, the maximal value for the respiratory exchange ratio in the patients was greater than 1.1 both pre- and posttransfusion suggesting that they closely approached, if not invariably achieved, a "true" $\dot{V}O_{2\text{max}}$. In this context, one advantage of the AT is that its measurement does not require a maximal effort.

It is noteworthy that reduced AT and rapid heart rate response during exercise are also observed in adult patients with congestive heart disease (20). In these patients, the low AT reflects the insufficient availability of O_2 in the periphery resulting from the reduced cardiac output. Our data provide evidence for a cardiac or pulmonary vascular impairment in some of the anemic patients.

Adaptation to reduced O_2 carrying capacity of anemia can be mediated in three ways: by an increase in 2,3-DPG facilitating O_2 unloading from hemoglobin (21), by increases in cardiac output, and by widening the arteriovenous O_2 content difference. Levels of 2,3-DPG in the patients studied were low for the degree of anemia. This has been observed in patients with thalassemia major by other investigators (22). The etiology of this depressed 2,3-DPG response remains unclear. Corraa *et al.* (23) have suggested that this lack of a red cell 2,3-DPG response may result in impaired O_2 delivery and a "functional anemia." As a consequence, the patients were dependent solely on adjustments of $\dot{Q}$ and arteriovenous O_2 content difference in order to maintain adequate O_2 delivery to the tissues.

Our data demonstrate that the cardiac adaptation for the anemia was a more rapid HR response to exercise (Fig. 5), as has been observed in subjects with anemia of other etiologies (24–26). This ability to adapt to the anemic state may explain why the increase in AT was small (9%) compared to the increase in Hb (22%) following transfusion. Moreover, in the older patients, whose HR during exercise were generally higher than normal both pre- and posttransfusion, the effect of transfusion was smaller than in the younger patients. This suggests that adaptation to anemia is diminished in the presence of heart or pulmonary vascular disease.

Transfusion improved the AT (Fig. 3) and the $\dot{V}O_2$ -HR relationship in the patients. The increase in AT was most likely due to the increase in arterial O_2 content following transfusion. This would result in higher pO_2 in the muscle tissue and facilitate O_2 transport into the cells. These observations are consistent with several previous studies in the literature. Thomson *et al.* (24) found improved O_2 transport attributed to increases in arterial O_2 tension following reinfusion of blood in normal subjects. Miller *et al.* (25) demonstrated increased anaerobic metabolism (excessive lactic acidemia) during exercise in patients with sickle-cell anemia. Finally, Woodson *et al.* (26) showed that $\dot{V}_E/\dot{V}O_2$ was higher in healthy subjects made anemic by phlebotomy. The lack of increase in the $\dot{V}O_{2\text{max}}$ in our patients may be explained by our not "pushing" the subjects at the higher work rates.

Despite the increase in AT following transfusion, both the

Fig. 5. Group mean response of HR as a function of $\dot{V}O_2$ before (dashed line) and after (solid line) transfusion in the 13 patients. Before transfusion, HR was faster at almost any $\dot{V}O_2$ during exercise.

$\dot{V}O_2$ max and the AT were significantly less than predicted (Figs 1–3). Only two of the patients had values of the AT greater than predicted following transfusion. Thus, a mild abnormality in gas exchange during exercise seems to be present even in some of the younger patients.

In contrast, the self-assessment of physical activity in the patients was comparable to normal children of the same age and gender. The discrepancy between this and the results of the exercise studies suggests several possible explanations. First, the physiologic abnormalities that we observed might not have been severe enough to inhibit the child's "natural" inclination for physical activity. If so, the cardiorespiratory and metabolic adaptations to normal levels of physical activity are impaired in the patients. Second, the self-assessment done by patients who undergo frequent hospitalizations and nightly chelation therapy might be inaccurate, and, in truth, their level of physical activity is below normal. Alternatively, the questionnaire may have accurately described the time spent by the patients in physical activity, but the actual work done by them during activity may have been less than in normal children.

The $\dot{V}O_2$ max, AT, and relationship between $\dot{V}O_2$ and HR deteriorated with increasing age (Fig. 2). In addition, the effect of the transfusion on the $\dot{V}O_2$ -heart rate slope was significantly less in the older patients. These data suggest that either the disease process itself, or the effects of iron overload in the myocardium or lungs (especially in the older patients who had not benefited from chelation therapy as early in their lives as had the younger subjects) results in progressive impairment of cardiorespiratory function in response to exercise. The noninvasive measurements described herein can be useful in the continuing evaluation of hypertransfusion and chelation therapy.

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REFERENCES

- Winslow RM 1982 Hypoxia and polycythemia: the optimal hematocrit. In: Sutton JR, Jones NL, Houston CS (eds) Hypoxia: Man at Altitude. Thieme-Verlag, New York, pp 40–42
- Woodson RD 1984 Hemoglobin concentration and exercise capacity. *Am Rev Respir Dis* 129(suppl):S72–S75
- Hyman CB, Ortega JA, Costin G, Landing BH, Lazerson J, Leimbrock S, Lurie P 1976 Management of thalassemia in Los Angeles. *Birth Defects* 12:43–52
- Modell B and Berdoukas V 1984 The Clinical Approach to Thalassemia. Grune & Stratton, London
- Hardisty RM 1976 Diamond-Blackfan anemia. In: Congenital Disorders of Erythropoiesis: Ciba Symposium. Elsevier, Amsterdam, pp 89–101
- Ehlers KH, Levin AR, Klein AA, Markenson AL, O'Loughlin JE, Engle MA 1981 The cardiac manifestations of thalassemia major: natural history, noninvasive cardiac diagnostic studies and results of cardiac catheterization. *Cardiovasc Clin* 11:171–186.
- Cooper DM, Mansell AL, Weiner MA, Berdon WE, Chetty-Baktaviziam A, Reid L, Mellins RB 1980 Low lung capacity and hypoxemia in children with thalassemia major. *Am Rev Respir Dis* 121:639–645.
- Keens TG, O'Neal MH, Ortega JA, Hyman CB, Platzker ACG 1980 Pulmonary function abnormalities in thalassemia patients on a hypertransfusion program. *Pediatrics* 65:1013–1017
- Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K 1984 Aerobic parameters of exercise as a function of body size during growth in children. *J Appl Physiol* 56:628–634
- Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K 1984 Growth-related changes in oxygen uptake and heart rate during progressive exercise in children. *Pediatr Res* 18:845–851
- Whipp BJ, Davis JA, Torres F, Wasserman K 1981 A test to determine parameters of aerobic function during exercise. *J Appl Physiol* 50:217–221
- Beaver WL, Lamarra N, Wasserman K 1981 Breath-by-breath measurement of true alveolar gas exchange. *J Appl Physiol* 51:1662–1675
- Wasserman K, Whipp BJ, Koyal SN, Beaver WL 1973 Anaerobic threshold and respiratory gas exchange during exercise. *J Appl Physiol* 35:236–243
- Hansen JE, Sue DY, Wasserman K 1984 Predicted values for clinical exercise testing. *Am Rev Respir Dis* 129(suppl):S49–S55
- Linnarsson D 1974 Dynamics of pulmonary gas exchange and heart rate changes at start and end of exercise. *Acta Physiol Scand [Suppl]* 415:1–68
- Wasi P, Fucharoen S, Youngchaiyud P, Sonakul D 1982 Hypoxemia in thalassemia. *Birth Defects* 18:213–217
- Landing BH, Nadorra R, Hyman CB, Ortega JA 1985 Pulmonary lesions of thalassemia major—their occurrence and significance. *Perspect Pediatr Pathol* (in press)
- Freeman AP, Giles RW, Berdoukas VA 1983 Early left ventricular dysfunction and chelation therapy in thalassemia major. *Ann Intern Med* 99:450–454
- Kupperman JL, Whipp BJ, Gardner GW, Wasserman K 1981 The effect of anemia on the ventilatory and gas exchange responses to exercise. *Am Rev Respir Dis* 123:196(abstr)
- Weber KT, Kinasewitz GT, Fishman AP 1982 Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circ* 65:1213–1223
- Torrance J, Jacobs P, Restrepo A 1970 Intraerythrocytic adaptation to anemia. *N Engl J Med* 283:165–169
- de Furia FG, Miller DR, Canale VC 1974 Red blood cell metabolism and function in transfused β -thalassemia. *Ann NY Acad Sci* 232:323–332
- Correra A, Graziano JH, Seaman C, Piomelli S 1984 Inappropriately lowered cell 2,3-diphosphoglycerate and p50 in transfused B-thalassemia. *Blood* 63:803–806
- Thomson JM, Stone JA, Ginsburg AD, Hamilton P 1982 O_2 transport during exercise following blood reinfusion. *J Appl Physiol* 53:1213–1219
- Miller GJ, Serjeant GR, Sivapragasam S, Petch MC 1973 Cardio-pulmonary responses and gas exchange during exercise in adults with homozygous sickle-cell disease (sickle-cell anemia). *Clin Sci* 44:113–128
- Woodson RD, Wills RE, Lenfant C 1978 Effect of acute and established anemia on O_2 transport at rest, submaximal and maximal work. *J Appl Physiol* 44:36–43