Circulatory Haemodynamics After Blood Transfusion in Chronic Severe Anaemia*

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In patients with chronic severe anaemia blood transfusion is often essential and the only life-saving procedure. It provides not only immediate relief of symptoms but prevents potential irreversible anoxic damage to tissues. Several investigators (Drummond, 1943; Sharpey-Schafer, 1945; Fullerton and Turner, 1962; Graettinger, Parsons, and Campbell, 1963) have, however, reported heart failure, pulmonary oedema, and deaths in patients with severe anaemia after transfusion of whole blood as well as of packed red cells, either given rapidly or slowly. It is believed that in anaemic patients the functional capacity of the myocardium may be severely impaired and its reserve powers negligible so that any overloading of circulation may then precipitate heart failure (Drummond, 1943). Dangers of circulatory overloading have therefore been stressed and suggestions have been made regarding the amount and the speed of blood transfusion in anaemic patients (Drummond, 1943; Wintrobe, 1961; Britton, 1963).

Reports of effects of blood transfusion on circulatory haemodynamics in patients with chronic severe anaemia are few, and the number of patients studied in these reports is small (Sharpey-Schafer, 1945; Regan *et al.*, 1963; Duke, Herbert, and Abelmann, 1964). The present investigation was, therefore, undertaken to determine the haemodynamic alterations and possible dangers of circulatory overloading after moderately rapid transfusion of whole citrated blood in patients with chronic severe anaemia, including patients with clinical heart failure, cardiac enlargement, or electrocardiographic abnormalities, and to determine the duration of haemodynamic alterations.

SUBJECTS AND METHODS

Studies were made on 38 patients, 21 male and 17 female, admitted to hospital for treatment of chronic severe anaemia and with haematocrit values of 20 per cent or less. Care was taken to exclude patients with any other cardiovascular disease apart from anaemia; and only patients with curable anaemia were selected. The ages ranged from 10 to 50 years, with an average of 30 years. The haematocrit values ranged from 6 to 20 per cent, with an average of 14 per cent; it was up to 12 per cent in 13, 13 to 16 per cent in 13, and 17 to 20 per cent in 12 patients. The aetiological factor of anaemia was ankylostomiasis in 18, chronic dysentery in 6, uterine bleeding in 6, bleeding haemorrhoids in 3 patients, and was unknown in 5 patients. The heart size was normal in 14, slightly enlarged in 11, and moderate to considerably enlarged in 13 patients. A 12-lead electrocardiogram was obtained in 34 patients and was abnormal in 19 of them. Clinical heart failure was present at the time of admission in 3 patients who were given digoxin in doses of one tablet 3 times a day for 24 to 48 hours before transfusion.

The data were obtained in every patient before and immediately after transfusion in the fasting state and in recumbent position. The data were obtained again one hour after transfusion in 10 patients and 6 hours after transfusion in 15 patients. All patients were watched closely after the transfusion for any evidence of aggravation of symptoms, dyspnoea, or of appearance of râles in the lungs.

Cardiac output was estimated by the dye-dilution method of Hamilton *et al.* (1948), using indigo-carmine. The blood was withdrawn from the femoral artery through a Gilford cuvette densitometer and the dye-dilution curve was recorded oscillographically. The blood volume was estimated by the method of Gibson and Evans (1937) using Beckman's spectrophotometer. Venous and arterial pressures were obtained in all cases. Right atrial pressures were obtained by cardiac catheterization in five cases. Pressures were recorded oscillographically by using a Statham strain-gauge transducer. Mean pressures were obtained by damping. Midway

TABLE I

DISTRIBUTION OF PATIENTS ACCORDING TO CARDIAC OUTPUT AND ITS
RELATION TO HEART SIZE BEFORE TRANSFUSION AND ALTERATIONS OF
OUTPUT AFTER TRANSFUSION

Cardiac output (l./min.)	Total number of patients	Heart size			Alterations of output after transfusion		
		Normal	Slight enlarge-ment	Moderate enlarge-ment	In-crease	De-crease	No change
< 7	11	6	3	2	9	2	0
7–10	18	8	6	4	10	6	2
> 10	9	0	2	7	3	5	1
Total	38	14	11	13	22	13	3

between the table top level and the sternal level was taken as the baseline for recording venous pressure. Central blood volume, total vascular resistance, and the left ventricular work were calculated by standard formulae.

Whole citrated blood was transfused at a rate of 7 to 16 ml./min., with an average of 10·5 ml. The amount ranged from 350 to 750 ml., with an average of 620 ml.

Alterations of more than 0·5 l. in cardiac output, 2 cm. H_2O in venous pressure, 5 mm. Hg in mean arterial pressure, 100 dynes in total vascular resistance, 5 ml. in stroke volume, 0·1 l. in central blood volume, 5 per minute in heart rate, and 0·5 kg.m. in left ventricular work were considered alterations for the purpose of this study.

TABLE II

MEAN VALUES OF DATA BEFORE AND AFTER TRANS-
FUSION AND SIGNIFICANCE OF ALTERATIONS

	Mean values		Significance values	
	Before trans-fusion	After trans-fusion	't' value	p value less than
Total blood volume (l.)	2·99	3·52	9·2	0·001
Cardiac output (l./min.)	8·63	9·5	3·4	0·01
Venous pressure (cm. H₂O)	11·4	14·8	2·9	0·01
Mean arterial pressure (mm. Hg)	80	91	2·38	0·05
Left ventricular work (kg./min./m².)	6·74	8·42	2·84	0·01
Heart rate/min.	78	88	2·3	0·05
Central blood volume (l.)	1·44	1·55	—	—
Stroke volume (ml.)	110	110	—	—
Total vascular resistance (dynes sec. cm².)	801	830	—	—

RESULTS

Before transfusion the cardiac output was more than 7 l./min. in 27 patients and less than 6 l./min. in only 4. The output values showed significant correlation to the cardiac size (p < 0·02), and output of more than 10 l. was seen only in patients with enlarged hearts (Table I). The venous pressure

was abnormally raised (16 cm. H_2O or more) between 16 and 19 cm. in 6 patients, including 3 with congestive failure. After blood transfusion total blood volume increased in every case. Other haemodynamic alterations were not consistent and the data showed either increase, decrease, or no changes. There were, however, significant increases in cardiac output, total blood volume, venous pressure, mean arterial pressure, heart rate, and left ventricular work (Table II), but no significant alteration in central blood volume, stroke volume, and total vascular resistance. The cardiac output increased in 22 patients, including 13 of 24 patients with cardiac enlargement and 7 of 19 with abnormal electrocardiograms. The incidence of alterations in output showed significant correlation to alterations in mean arterial pressure, total vascular resistance, left ventricular work, and stroke volume (p < 0·001), and no relation to alterations in venous pressure, central blood volume, heart rate, haematocrit values, or heart size. The venous pressure increased in 23 patients with increases in output in 12 of them. Right atrial pressures, which were obtained in 5 patients, showed increases in 3 of them after transfusion, with increases in output in 2 of these 3. Alterations in cardiac output and the central blood volume showed no relation to initial normal or abnormal venous pressure or to changes in venous pressure after transfusion (Table III).

The observations were repeated one hour after transfusion in 10 patients. The total blood volume decreased in 9 and venous pressure in 8 patients. The mean values before transfusion, after transfusion, and one hour after transfusion, respectively, of total blood volume were 2·87, 3·47, and 3·20 l., and of venous pressure 12·8, 16·4, and 13·6 cm. Other alterations were minor.

When observations were repeated 6 hours after transfusion in 15 patients, there was no uniformity in the haemodynamic alterations. The mean values of the data before, immediately after, and 6 hours

TABLE III
RELATION BETWEEN VENOUS PRESSURE AND INCIDENCE OF ALTERATIONS IN CARDIAC OUTPUT AND CENTRAL BLOOD VOLUME

	Total number of patients	No. of cases					
		Cardiac output			Central blood volume		
		In-crease	De-crease	No change	In-crease	De-crease	No change
Venous pressure before transfusion							
Normal	32	19	10	3	17	9	6
Abnormal	6	3	3	0	3	0	3
Venous pressure after transfusion							
Normal	20	12	6	2	9	6	5
Abnormal	18	10	7	1	11	3	4

after transfusion are given in Table IV. There were significant reductions in venous pressure ($p < 0.02$), with return to pretransfusion levels in 14 patients. The total blood volume decreased in 14 patients but remained slightly higher than the pre-transfusion level in 9 of them. It increased in one patient. Although haemodynamic measurements showed no statistically significant alteration, there were reductions in cardiac output, mean arterial pressure, central blood volume, and left ventricular work with return to pretransfusion levels or less in the majority of patients (Table IV).

DISCUSSION

There is no agreement about haemodynamic changes that occur after blood transfusion in patients with chronic severe anaemia and in normal subjects. Sharpey-Schafer (1945), Frye and Braunwald (1960), and Duke et al. (1964) observed no consistent haemodynamic changes, but Regan et al. (1963) found a consistent increase in cardiac output, mean arterial pressure, and left ventricular work after transfusion. The present study also showed no consistent pattern of haemodynamic alterations immediately after transfusion, except that the total blood volume increased in every case. The central blood volume, venous and mean arterial pressure, left ventricular work, stroke volume, and heart rate increased in the majority of the patients, but in others either decreased or showed no change. Frye and Braunwald (1960) suggested that the difference in the response of the central blood volume may explain failure of consistent augmentation of cardiac output. In our study the changes in central blood volume did not have any relation to changes in the cardiac output. Duke et al. (1964) noted that central blood volume invariably increased in patients with normal venous pressure, in sharp contrast to its decrease in patients with abnormally

raised venous pressure before transfusion. In our study, the changes in central blood volume showed no relation to raised venous pressure either before or after blood transfusion (Table III).

Sharpey-Schafer (1945) and Duke et al. (1964) noted that cardiac output decreased after transfusion in those patients who had abnormally raised right atrial or venous pressure before transfusion, despite further increases in venous filling pressure. Graettinger et al. (1963), however, reported a decrease in output in a patient with normal venous pressure before transfusion, despite a steady rise of right atrial pressure after transfusion. They also noted further increases in output in response to exercise in 2 patients with anaemia even in the pres-

TABLE IV
MEAN VALUES OF DATA BEFORE, IMMEDIATELY AFTER, AND SIX HOURS AFTER TRANSFUSION IN 15 PATIENTS AND NUMBER OF PATIENTS WHOSE VALUES RETURNED TO PRETRANSFUSION LEVELS OR LESS AFTER 6 HOURS

	Mean values			No. of patients
	Before trans-fusion	After trans-fusion	After six hours	
Cardiac output (l./min.)	8·97	10·03	8·37	11
Central blood volume (l.)	1·44	1·67	1·44	11
Total blood volume (l.)	2·55	3·08	2·83	6
Venous pressure (cm.H_2O)	12·1	16·5	12·2	14
Mean arterial pressure (mm. Hg)	78	92	83	9
Left ventricular work (kg./min./m²).	6·85	8·84	7·05	9

ence of cardiac failure and raised right atrial pressure. Sharpey-Schafer (1945) suggested that in severe anaemia the heart behaved like Starling's over-loaded heart-lung preparation, so that if the venous filling pressure were already high, a further rise in pressure after transfusion would result in a falling cardiac output. Duke et al. (1964) also suggested that transfusion was well tolerated if venous pres-

sure were normal but an initial increase in venous pressure was associated with poor tolerance of transfusion, cardiac output falling notwithstanding further increases in venous filling pressure. Sharpey-Schafer (1945) and Duke et al. (1964) therefore stressed the importance of monitoring venous filling pressure during transfusion. Duke et al. (1964) even suggested removal of blood if there was a further increase in pressure after transfusion in patients with raised venous pressure. In our study the venous pressure increased in 23 patients after transfusion, but the cardiac output increased in only 12 of them. Again, the output increased in 3 of 6 patients with initial abnormal venous pressure, including 2 with cardiac failure on admission and 7 of 12 others with abnormal increases in pressure after transfusion. Our study, therefore, showed that there was no relation between increases in cardiac output and in venous pressure; thus, Starling's law that cardiac output increases with increase of venous filling pressure was often not applicable in our patients. It also showed that the changes in cardiac output were not related to the venous pressure either before or after transfusion.

Graettinger et al. (1963) have reported increases in cardiac output in response to exercise in anaemic patients with cardiac enlargement. In our study the output increased in 7 patients with slight and 6 patients with moderate cardiac enlargement, and in 7 patients with abnormal electrocardiograms. Thus, the heart in anaemia was often capable of further augmenting the cardiac output significantly in reponse to blood transfusion, even in the presence of enlargement and electrocardiographic changes. These two methods of assessment cannot, therefore, be considered as guides for the evaluation of cardiac reserve or function as determined by the cardiac output response to transfusion.

The present study showed significant correlation between cardiac output and cardiac size before transfusion, the output being higher with greater cardiac size. The alterations in output after transfusion showed no significant relation to the heart size, the initial cardiac output, or to the haematocrit values. It was noted, however, that the incidence of increase in output was comparatively less in patients with higher initial output values, that the amount of increase in output was significantly less in those patients with lower haemotocrit values, and that the increase in output was mostly the result of an increase in stroke volume. The findings suggest that Starling's law of the heart that the cardiac output increases in relation to increased stretch of the cardiac muscle fibres associated with increased cardiac size in anaemic patients is usually applicable when they are resting. In response to transfusion

the alterations in output probably depend upon the interplay of several factors, including haematocrit values and cardiac size and output before transfusion, and changes in the venous pressure and the stroke volume after transfusion. Failure of a constant circulatory response to blood transfusion in normal subjects has been attributed by Frye and Braunwald (1960) to the intact autonomic nervous system, as they observed consistent increases in cardiac output in the same subjects after administration of ganglionic blocking agents before transfusion.

Reports of pulmonary oedema or deaths attributed to circulatory overloading after transfusion in anaemic patients have been published. The danger of heart failure has been stressed (Drummond, 1943; Sharpey-Schafer, 1945; Fullerton and Turner, 1962; Graettinger et al., 1963) and is mentioned in textbooks of haematology (Wintrobe, 1961; Britton, 1963). Drummond (1943) reported cases of circulatory failure after rapid transfusion of 120 to 2700 ml. at rates of 1·1 to 18 ml./min., necropsy showing cardiac dilatation, pulmonary congestion, and oedema, indicating left heart failure. Sharpey-Schafer (1945) reported the appearance of pulmonary oedema in 2 patients who received 530 and 510 ml. packed cells at rates of 13 and 29 ml./min., respectively, with death in the second case. Fullerton and Turner (1962) reported a high incidence of failure and mortality in pregnant women with anaemia after transfusions of 250 to 500 ml. of packed cells within 3 to 8 hours. They therefore recommended exchange transfusions of blood in severely anaemic pregnant women. In their patients, however, labour was imminent, and failure occurred during or within a few hours of labour, and it is not unlikely that the stress of labour itself was responsible for untoward reaction and not the transfusion. Regan et al. (1963), however, noted no cardiac handicap after rapid transfusion of 800 ml. packed red cells at a rate of 18 ml./min. in 6 anaemic patients. In the present study circulatory overloading with increases of blood volume, venous pressure, mean arterial pressure, and left ventricular work did occur in the majority of patients. There was, however, not a single instance of aggravation of symptoms or of dyspnoea, though pulmonary râles appeared at bases without any dyspnoea in one patient who had clinical heart failure on admission. This finding is particularly significant because some of our patients had either initial or subsequent abnormally high venous pressure, clinical failure, moderate to considerable cardiac enlargement, or electrocardiographic changes, and had received transfusion of whole blood and not of packed cells at a moderately rapid rate. It is concluded, therefore, that administration of a pint of

whole blood in the course of about one hour is not associated with any risk. Duke *et al.* (1964) suggested that if there were further increases in venous filling pressure after transfusion in patients with abnormally raised pressures before transfusion, blood should be removed to restore the haemodynamic findings to pretransfusion levels, though they did not observe any aggravation of symptoms or any change in physical signs in these patients. We find no justification for such a procedure, because the patient will be deprived of the only therapeutic measure which rapidly reverses the dangerous oxygen lack in very severe anaemia.

A significant decrease of myocardial blood flow despite an increase of cardiac output has been observed by Regan *et al.* (1963) after transfusion of packed red cells in patients with anaemia. They postulated that this represented the influence of a highly viscous red cell mass. It is not unlikely that this decrease of myocardial blood flow may result in further impairment of ventricular function. We, therefore, recommend that transfusion of whole blood and not of packed red cells should be given to patients with severe anaemia. This will also supply plasma proteins, usually deficient in such patients.

Repeat studies after one and six hours showed that the circulatory overloading was short lived, which may explain the absence of unfavourable reactions. The total blood volume and venous pressure began decreasing within an hour, and six hours after transfusion, the venous and mean arterial pressures, the cardiac output, and the left ventricular work had regressed, in the majority of cases, to pretransfusion levels.

SUMMARY

Circulatory haemodynamics were studied in 38 patients with chronic severe anaemia before and immediately after blood transfusion, and in 10 patients one hour after, and in 15 patients 6 hours after transfusion. Patients included some with cardiac enlargement, electrocardiographic abnormalities, or clinical heart failure. Whole citrated blood was transfused: the amounts ranged from 350 to 750 ml., with an average of 620 ml., and the rate ranged from 7 to 16 ml./min., with an average 10·5 ml.

The cardiac output before transfusion showed significant correlation with the cardiac size, the output being higher with greater cardiac size. After transfusion the total blood volume increased in every case. There was no consistent pattern of other haemodynamic alterations. There was a significant increase in cardiac output, venous and mean arterial pressure, heart rate, and left ventricular work. There was no significant alteration in central blood volume, stroke volume, and total vascular resistance.

The alterations in cardiac output showed significant correlation with the alterations in mean arterial pressure, total vascular resistance, and stroke volume. They were not found to have any relation to alterations in venous pressure, central blood volume, or other factors. They also showed no relation to the venous pressure either before or after transfusion.

There was not a single instance of aggravation of symptoms or of dyspnoea after transfusion. Pulmonary râles without dyspnoea appeared in one patient who had clinical heart failure on admission.

The haemodynamic alterations began to regress within an hour and had returned to normal in most patients after six hours.

It is concluded that blood transfusion, within the limits of the amount and the rate in this study, is devoid of any risk due to circulatory overloading in anaemic patients.

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