Effects of intravascular fetal blood transfusion on fetal intracardiac Doppler velocity waveforms

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In 12 fetuses from pregnancies with red blood cell isoimmunization Doppler velocity waveforms were recorded at the level of atrioventricular valves immediately before and at 15-minute intervals for 2 hours after the intravascular transfusion. The left and right cardiac outputs, the ratio between the peak velocities during early passive ventricular filling and active atrial filling at the level of both ventricles as well as the heart rate were calculated. Before transfusion, the left and right cardiac outputs were significantly higher than reference ranges for gestation that were constructed from the cross-sectional study of 187 normal pregnancies. After transfusion there was a significant temporary fall in right and left outputs associated with increased ratios between the peak velocities during early passive ventricular filling and active atrial filling. Within 2 hours after transfusion both parameters returned toward the normal range. In addition, no significant changes were found for fetal heart rate values before and after transfusion. The fall of cardiac output was significantly related to the amount of expansion of the feto-placental volume. (AM J OBSTET GYNECOL 1990;163:1231-8.)

Key words: Red blood cell isoimmunization, intrauterine intravascular transfusion, cordocentesis, fetal echocardiography, Doppler ultrasonography

Intravascular fetal blood transfusion by cordocentesis represents a significant improvement in the treatment of red blood cell isoimmunization.[1] However, to limit the risks of repeated procedures and to shorten the duration of the transfusion the amount of blood transfused is usually high with respect to the estimated fetoplacental blood volume and is injected rapidly.

Up to now few data are available on the effects of such treatment on fetal hemodynamics.[3, 4] The advent of Doppler echocardiography has made it possible to study intracardiac blood flow velocity waveforms in the human fetus and to obtain reliable assessment of cardiac output.[5, 6] We therefore examined the effect of intravascular blood transfusion on cardiac hemodynamics in a group of fetuses from pregnancies with red blood cell isoimmunization.

Material and methods

Twelve pregnancies complicated by red blood cell isoimmunization undergoing intravascular transfusion were considered for this study. All pregnancies were singleton and accurately dated by certain last menstrual period and early ultrasonographic examination. All the fetuses had been previously transfused and the time interval from the preceding transfusion ranged between 2 and 4 weeks. The criteria followed for the timing of transfusions has been reported in detail elsewhere.[1] Although none of the fetuses had ultrasonographic evidences of hydrops, in all the cases the fetal hemoglobin concentration was below the second SD (mean difference, −3.62 SD; range, −2.43 to −5.16 SD) of our reference range for gestation.[7]

The mean (± SD) gestational age at the time of the study was 31.42 ± 3.18 weeks (range, 26 to 37). Before transfusion all patients gave their informed consent to participate in the study.

Doppler recordings. Commercially available Acuson 128 color Doppler equipment (Acuson, Montain View, Calif.) with 3.5 or 5 MHz sector probes was used for all measurements. Recordings were performed with the mother lying in a comfortable semirecumbent position. All the recordings were performed by one operator (G. R.) and the technique used has been reported in detail.[8] Briefly, an apical four-chamber view of the fetal heart was first obtained. The color flow mapping function was then superimposed and the transmitral and transtricuspid flow observed. The sample volume was placed immediately below either the mitral or tricuspid valves in the point of maximum flow velocity, as ex-

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Table I. Hematologic values measured before and after intravascular transfusion

Case no.	*Gestation (wk)*	*Pretransfusion hemoglobin (gm/dl)*	*Pretransfusion hematocrit (%)*	*Posttransfusion hemoglobin (gm/dl)*
1	30	10.3	31.1	16.2
2	33	9.9	29.1	17.3
3	32	10.4	30.3	17.0
4	35	12.0	34.7	16.1
5	26	8.5	24.9	15.2
6	31	9.6	28.7	17.1
7	31	10.4	30.3	15.0
8	37	12.5	39.4	15.9
9	32	10.4	31.4	15.8
10	27	8.9	26.5	15.3
11	34	9.2	27.8	16.9
12	29	10.9	31.3	14.8
Mean	31.42	10.25	30.46	16.05
SD	3.18	1.17	3.80	0.87

Table II. Left and right cardiac output in healthy fetuses (control) and in anemic fetuses before and 2 hours after intravascular transfusion

	Control	*Pretransfusion*	*Posttransfusion*
LVO (ml/min/kg)	249.12 ± 94.23	364.57 ± 121.18	300.73 ± 98.36
RVO (ml/min/kg)	295.45 ± 97.41	398.76 ± 111.44	346.41 ± 94.35

LCO, Left cardiac output; *RCO*, right cardiac output.

Control versus pretransfusion, $p \leq 0.01$ (the unpaired Student t test). Pretransfusion versus posttransfusion, $p \leq 0.01$ (the paired Student t test).

pressed by the color brightness, and velocity waveforms were then recorded. Doppler and two-dimensional images were recorded on standard ½-inch videotape for subsequent analysis. Recordings were performed immediately before (0) and at 15-minute intervals for 2 hours after the intravascular transfusion (+15, +30, +45, +60, +75, +90; +105, +120). Recordings obtained with an angle of insonation >30° or during periods of fetal body and breathing movements were rejected.

Atrioventricular valve diameters were evaluated from the two-dimensional images obtained from optimal apical four-chamber views. Measurements were performed in playback on video-recorded images frozen during diastole when showing the maximized diameters. Measurements were repeated on 10 different cycles for each valve and the values obtained were averaged. Repeated diameter measurements varied <0.6 mm for either valve. Valvular area was calculated assuming a circular cross-section.

Permanent records of all the velocity waveforms were obtained from the videotape by means of a strip chart recorder. The printouts were labeled with random numbers. The observer involved in the later analysis was not informed of the sequence of the printouts. Ten consecutive velocity waveforms were selected for each time interval from both atrioventricular valves and measurements of the following variables were made by use of the digitizing tablet of a computer (Cardio 800, Kontron, Oxford, England): (1) peak velocities during early ventricular filling (E wave) and atrial contraction (A wave); (2) mean temporal velocity; (3) fetal heart rate.

For each time interval a ratio between E peak and A peak velocities (E/A ratio) at the level of both atrioventricular valves was calculated. Absolute right and left cardiac outputs (milliliters per minute) were derived by multiplying the tricuspid or mitral mean temporal velocities, valvular area, and heart rate. The ratio between right and left cardiac output was then calculated. Cardiac output was also expressed as milliliters per minute per kilogram. The fetal weight was estimated from the ultrasonographic measurements of fetal biparietal diameter and abdominal circumference[9]; in all the cases abdominal circumference values ranged between the 10th and 90th percentile of our reference limits.

The data of the fetuses with red blood cell isoimmunization were compared with reference ranges constructed on the cross-sectional study of 187 fetuses from normal pregnancies between 20 and 40 weeks' gestation.

Posttransfusion hematocrit (%)	*Blood volume transfused (ml)*	*Transfusion rate (ml/min)*	*Expansion (%)*	*Expansion rate (%/min)*
48.5	80	14	63.74	11.15
51.5	150	7.9	93.72	4.94
44.1	100	20	61.06	12.21
46.4	110	7.3	36.34	2.41
43.9	80	5	99.48	6.22
50.4	120	15	106.37	13.30
44.1	100	8.3	61.06	5.07
50.9	160	9.4	79.19	4.65
47.8	70	5.8	49.55	4.11
45.6	60	15	65.86	16.47
50.9	100	12	62.60	7.51
46.4	70	16	48.64	12.07
47.54	100.00	11.30	69.87	8.34
2.87	31.33	4.7	21.54	4.49

In our laboratory the intraobserver coefficient of variation for all the measurements considered is <12%.

Method of transfusion. Intravascular fetal blood transfusion was performed in accordance with a previously described technique without maternal sedation or fetal paralysis.[1] The site and direction of the umbilical cord at its placental insertion was defined by real-time ultrasonographic scanning and a 20-gauge needle was inserted in the umbilical vein. A 2 ml sample of fetal blood was aspirated for measurement of hemoglobin (Coulter S Plus counter, Coulter Electronics Ltd., Luton, England) and blood gases (ABL 30 blood gas analyser, Radiometer, Copenhagen, Denmark). Fetal transfusion was performed with packed red blood cells compatible with the mother (mean hematocrit, 73.43%; SD, 7.18%; range, 63.0% to 87.8%). At the end of the transfusion the needle was flushed with normal 0.5 ml of saline solution and after 1 minute a sample of fetal blood was aspirated. The first 0.5 ml were discarded and the posttransfusion hemoglobin and hematocrit were subsequently evaluated.

The fetoplacental volume was determined as previously reported[2] and the percentage of its expansion after the transfusion was calculated: % Expansion = (Blood volume transfused/fetoplacental blood volume) × 100. Furthermore, we evaluated the expansion rate: (Expansion rate = Transfusion rate/fetoplacental blood volume) × 100.

Statistical analysis. The changes of E/A ratios, left cardiac output, right cardiac output, and heart rate were evaluated as the percentage change from the values obtained before transfusion (basal values). Data obtained at each time interval were averaged and reported as mean values ± 1 SD. Statistical analysis was performed with the use of analysis of variance for repeated measurements and the paired and unpaired student *t* test as indicated in the text. Relationships between the variables considered were tested by stepwise regression analysis. These analyses were performed on a Macintosh II computer with the Stat View II statistical package (Abacus Concepts Inc., Berkeley, Calif.).

Results

Intravascular transfusion was successful in all the fetuses studied and the individual hematologic values measured before and after transfusion are shown in Table I. Blood gas analysis performed before transfusion revealed Po_2, Pco_2, and pH values within 95% confidence interval of our reference ranges for gestation.[11]

Reliable recordings of right cardiac output and left cardiac output were obtained respectively 93.5% and 90.7% of the cases.

The prefusion values of left cardiac output, right cardiac output, and ratio of right cardiac output to left cardiac output of the fetuses with red blood cell isoimmunization are plotted on our reference ranges for gestation (mean and 95% confidence intervals) in Fig. 1. After correction for fetal weight the right cardiac output and left cardiac output were significantly higher (the unpaired Student *t* test, $p \leq 0.01$) than in the control group (Table II). Furthermore there was a tendency for the E/A ratios of both atrioventricular valves to be higher than those in our normal controls (Fig. 2) but this did not reach statistical significance.

After transfusion the right cardiac output and left cardiac output fell. Subsequently there was an increase in both parameters but to less than pretransfusion values (Fig. 3). Analysis of variance demonstrated the significance of these changes for both right cardiac output [$F(10,100) = 16.13, p \leq 0.001$] and left cardiac output [$F(10,97) = 13.47, p \leq 0.001$]. Significant differences

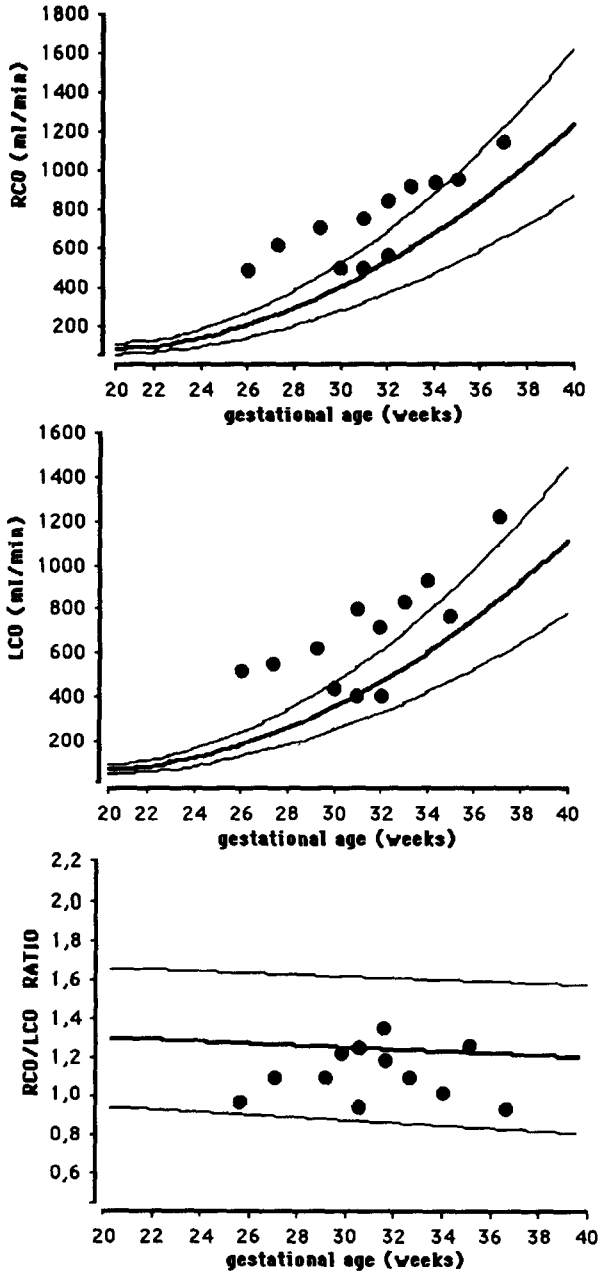

Fig. 1. Right cardiac output *(RCO) (top)*, left cardiac output *(LCO) (middle)*, and *RCO/LCO (bottom)* values obtained before transfusion plotted on our reference ranges for gestation (mean and 95% confidence intervals).

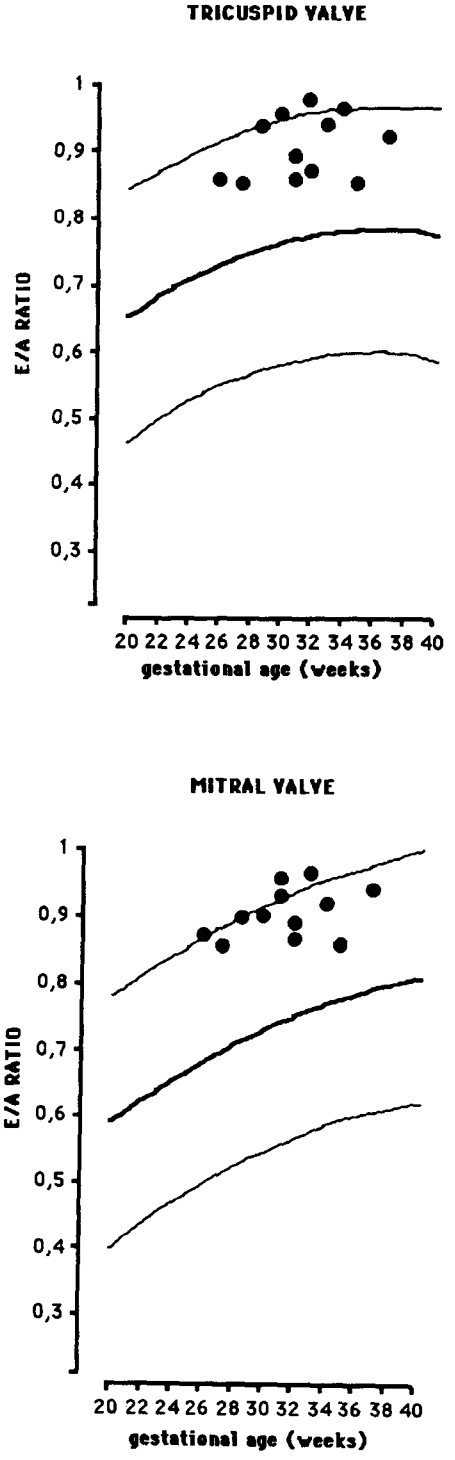

Fig. 2. Transtricuspid and transmitral E/A ratio values obtained before transfusion plotted on our reference ranges for gestation (mean and 95% confidence intervals).

were found (the paired Student t test) between pretransfusion values of right cardiac output and left cardiac output and +15, +30, +45, +60, +105, +120 values. Furthermore the E/A ratios were significantly modified after transfusion [tricuspid valve $F(10,100) = 8.21$, $p \leq 0.001$; mitral valve $F(10,97) = 4.59$, $p \leq 0.01$]. The highest value of E/A ratio were found at +15 minutes and then progressively returned toward basal values (Fig. 4).

No significant changes were found after transfusion for the ratio of right cardiac output to left cardiac output [$F(10,96) = 0.98$, NS] or fetal heart rate [$F(10,100) = 1.42$, NS]. The individual data obtained before and at the +15-, +30-, and +120-minute in-

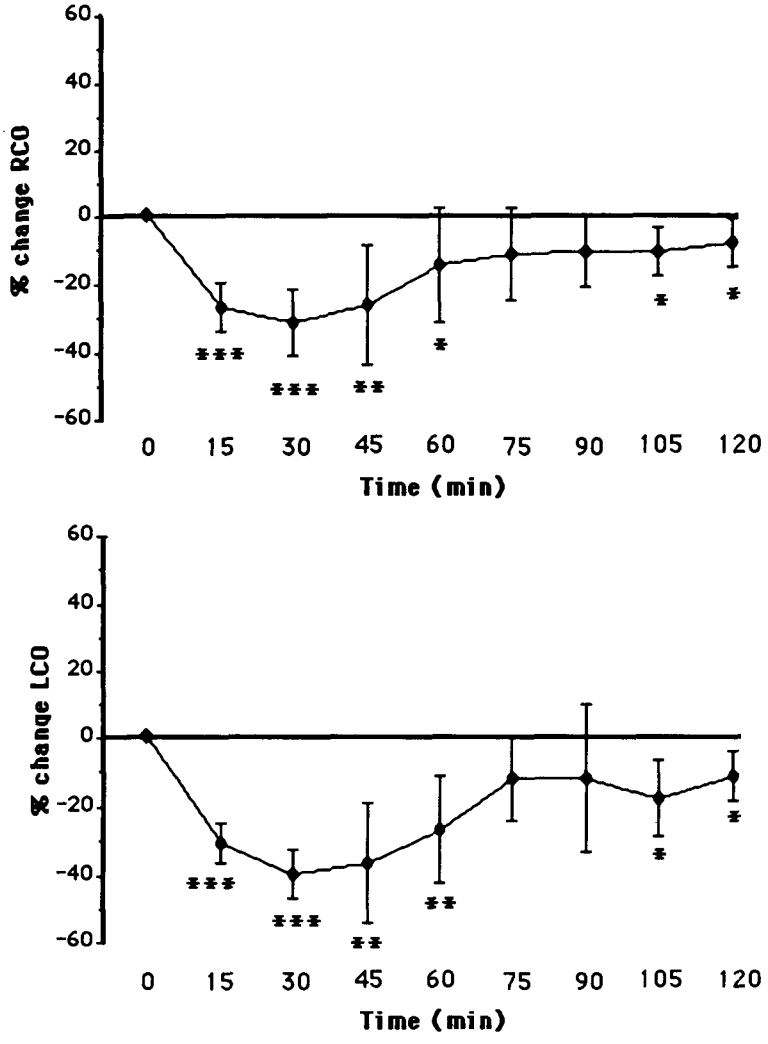

Fig. 3. Mean percentage changes (± 1 SD) of right cardiac output *(RCO)* and left cardiac output *(LCO)* after transfusion. Differences on comparison with pretransfusion values were evaluated by means of the paired Student *t* test (* = $p \leq 0.01$; ** = $p \leq 0.002$; *** = $p \leq 0.001$).

tervals after intravascular transfusion are provided in Table III.

Stepwise regression analysis revealed a significant linear correlation between the percentage of expansion of the fetoplacental blood volume (independent variable) and the maximum individual percentage fall of combined cardiac output (left cardiac output + right cardiac output) after transfusion (dependent variable); $r = 0.77$, $p \leq 0.01$, slope = 0.22, intercept, −21.01. There were significant correlations between the other Doppler parameters measured and either the volume of blood transfused or the percentage of expansion or the rate of expansion of the fetoplacental blood volume.

Comment

Our findings of increased fetal cardiac output in pregnancies with red blood cell isoimmunization is in agreement with previous reports on both the animal and the human fetus.[11-13] Although the mechanisms that cause the increase of cardiac output are still unclear two main factors have been suggested in animals[11]: first, decreased blood viscosity leading to increased venous return and cardiac preload, and second, peripheral vasodilatation as a result of a fall in blood oxygen content and therefore reduced cardiac afterload.

Previous studies in red blood cell isoimmunization have shown an increase of blood flow velocities from different fetal peripheral vessels including umbilical vein,[14] descending aorta,[3, 4, 15] and common carotid artery,[4] and the increase of velocity was related to the severity of anemia. The high pretransfusion E/A ratios found in this investigation suggest that cardiac preload is increased.[13] Furthermore, because the right cardiac output to left cardiac output ratio was normal there is no evidence for a redistribution of cardiac output sim-

Table III. Doppler echocardiographic measurements before and 15, 30, and 120 minutes after intravascular transfusion

Case no.	*Pretransfusion*						*Posttransfusion (+15 min)*					
	Tricuspid valve			*Mitral valve*			*Tricuspid valve*			*Mitral valve*		
	RCO	*HR*	*E/A*	*LCO*	*HR*	*E/A*	*RCO*	*HR*	*E/A*	*LCO*	*HR*	*E/A*
1	507	142	0.95	411	145	0.91	446	147	1.07	306	150	1.06
2	911	143	0.94	833	143	0.96	694	132	1.29	528	143	1.34
3	844	128	0.98	718	133	0.89	595	143	1.22	507	143	1.10
4	950	141	0.85	763	143	0.86	683	143	1.20	548	146	1.18
5	490	136	0.86	512	146	0.87	307	143	1.20	308	143	1.16
6	751	136	0.89	801	143	0.96	478	120	1.00	456	128	1.10
7	495	136	0.86	394	133	0.93	385	154	1.15	281	150	1.24
8	1136	130	0.92	1222	148	0.94	—	—	—	—	—	—
9	549	135	0.87	407	140	0.87	388	136	1.11	314	140	1.08
10	604	148	0.85	538	145	0.86	457	148	1.13	370	145	1.04
11	925	139	0.96	890	148	0.92	716	141	0.94	651	146	0.86
12	689	136	0.93	614	132	0.89	481	136	1.11	421	132	1.08

LCO, Left cardiac output; *RCO*, right cardiac output; *HR*, heart rate.

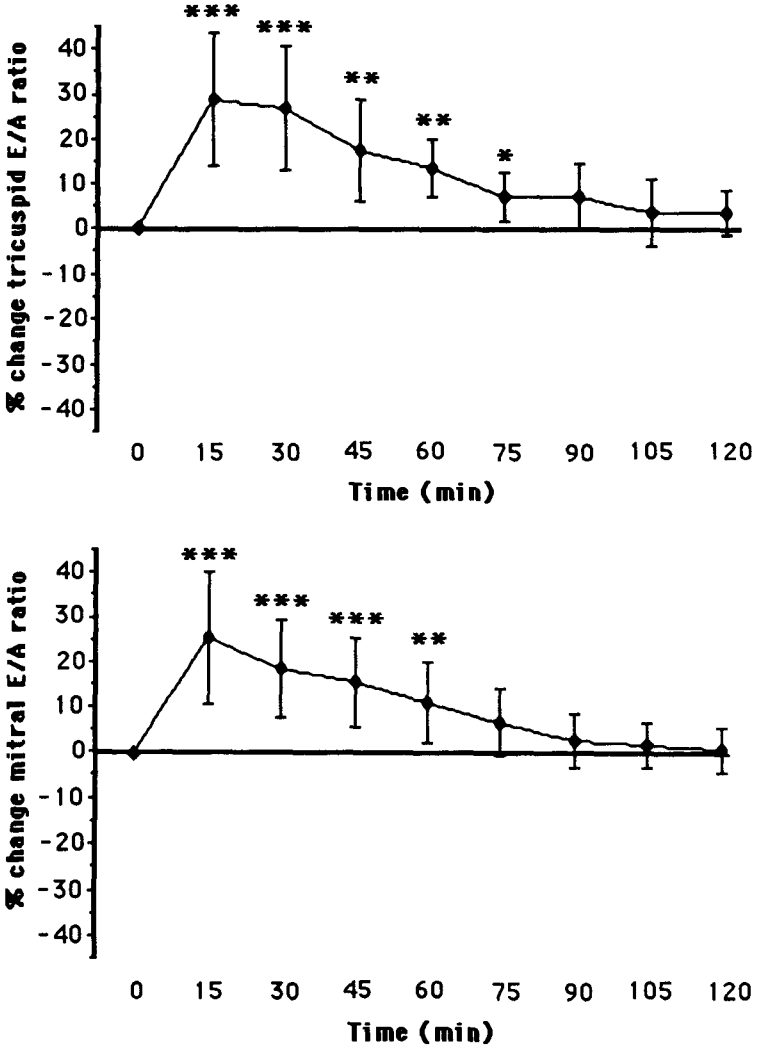

Fig. 4. Mean percentage changes (± 1 SD) of transtricuspid and transmitral E/A ratios after transfusion. Differences on comparison with pretransfusion values were evaluated by means of the paired Student *t* test (* = $p \leq 0.01$; ** = $p \leq 0.002$; *** = $p \leq 0.001$).

Posttransfusion (+30 min)						*Posttransfusion (+120 min)*					
Tricuspid valve			*Mitral valve*			*Tricuspid*			*Mitral valve*		
RCO	*HR*	*E/A*	*LCO*	*HR*	*E/A*	*RCO*	*HR*	*E/A*	*LCO*	*HR*	*E/A*
381	149	1.02	290	147	1.02	444	143	0.97	367	145	0.94
553	136	1.26	459	128	1.20	803	135	0.94	—	—	—
595	130	1.17	438	133	1.08	737	125	0.97	523	122	0.92
645	150	1.18	467	150	1.04	877	146	0.89	636	150	0.90
265	150	1.19	284	150	1.10	—	—	—	—	—	—
459	133	0.97	369	125	1.08	682	135	0.92	722	140	1.02
338	158	1.15	288	162	1.17	416	140	0.92	348	130	0.94
769	130	1.19	744	133	1.09	969	128	1.00	1017	120	0.95
430	133	1.04	224	133	0.98	467	130	0.95	387	135	0.87
381	147	1.09	308	142	1.07	581	141	0.80	507	144	0.87
594	139	0.97	601	138	0.85	936	131	0.87	847	129	0.84
504	138	1.12	351	133	1.07	728	133	0.96	572	140	0.87

ilar to that described in hypoxic growth-retarded fetuses (i.e., the so-called "brain sparing effect").[7] These findings suggest that in red blood cell isoimmunization the changes in fetal cardiac output are mainly related to the low blood viscosity.

Intravascular fetal blood transfusion was associated with a rapid decrease in cardiac output that was primarily the result of decrease in stroke volume rather than heart rate. These changes were similar in both ventricles and reached a nadir at 15 to 45 minutes after the transfusion. Thereafter the cardiac output increased but still remained below the pretransfusion level.

These findings are compatible with the observations of Bilardo et al.[4] who measured the time-averaged mean velocity in the fetal descending thoracic aorta and common carotid artery before and within 30 minutes of intravascular transfusion and found a significant decrease in both vessels.

A possible explanation for posttransfusion decrease in cardiac output is reduced venous return to the heart secondary to the increased hematocrit and therefore viscosity of blood or secondary to the release of vasodilators such as prostacyclin or atrial natriuretic factor.[16, 17] However, this is unlikely because the relative E/A ratios found after the transfusion suggest that cardiac preload is increased rather than decreased. Furthermore, if the decrease in cardiac output was because of increased hematocrit, this effect would be sustained for at least 24 hours. Copel et al.[12] measured velocities in the aorta and also cardiac output at 12 hours after intravascular blood transfusion and found no significant differences from the pretransfusion levels. Finally, the reported increase of umbilical venous pressure after intravascular transfusion[18, 19] does not support the hypothesis of a venous vasodilatation as the cause of a reduction in venous return.

The alternative explanation for the posttransfusion fall in cardiac output is cardiovascular overload. This is supported by the findings of a direct relationship between the fall in cardiac output and the degree of expansion of the fetoplacental blood volume. Animal studies have shown that the fetal heart has very limited reserve capacity to increase its output in response to acute overload[18] and that massive increases in fetal blood volume are associated with a decrease in cardiac output.[19] After a transfusion there is a rapid rate of fluid loss[20] and this explains the rapid recovery in E/A ratios and cardiac output.

Doppler echocardiography provides a reproducible method for the measurement of cardiac output in the human fetus.[5, 6] However, this analysis is prone to errors mainly because of inaccuracies in the determination of valve diameters that are halved and squared in the calculation of cardiac output and thus amplified. Nevertheless in our investigation the flow orifice area is assumed to remain unmodified and therefore potential errors in assessment of valve diameters would affect similarly the measurements performed during the study without impairing the reliability of the results obtained.

In conclusion, fetal anemia is associated with increased cardiac output. Rapid intravascular blood transfusion causes a temporary and symmetrical decrease in right cardiac output and left cardiac output that is proportional to the degree of expansion in fetoplacental blood volume.

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