Dye Dilution Curves and Cardiac Output in Newborn Infants

By Klara J. Prec, M.D. and Donald E. Cassels, M.D.

The pattern of dye dilution curves and the cardiac output was studied in 29 healthy newborn infants during the first 26 hours of life by the method of Wood and his associates. Thirty-six per cent of all infants studied had curves of normal contour which occurred mostly in infants older than 15 hours. Infants younger than 15 hours tended to have curves of abnormal shape. These were either diphasic or had the appearance of curves associated with left-to-right shunts and were probably caused by a patent ductus arteriosus. The mean cardiac output was 540 cc per minute.

The study of the physiology of the cardiovascular system in newborn infants has been limited because of the technical difficulties encountered in trying to apply methods used in adults. The dye dilution method of Hamilton¹ ² ³ as modified by Wood and his associates⁴ ⁵ ⁶ seemed to be a relatively simple approach to the study of these problems. We have used this method to study the pattern of dye dilution curves and to determine the cardiac output of infants during the first two days of life. We believe that the results obtained from the study of the contour of dye dilution curves and the relationship of the various components of these curves also give information that may be of help in detecting the persistence of one or more fetal channels during the early neonatal period.

Material

Twenty-nine healthy newborn infants, age 2 to 26 hours, were included in the study. Each infant was studied asleep with its head and chest placed under an “oxyhood” into which oxygen was delivered at a flow of 7 liters per minute. Infants who were restless or crying were not included in the study.

Method

A Brush recorder was used in conjunction with the Wood earpiece oximeter for the continuous recording of the dilution pattern of Evans-blue dye (T-1824) following almost instantaneous injection of this dye into the umbilical vein. The single scale method only was used. The amount injected was calculated on the basis of 0.4 to 0.5 mg per kilogram of body weight and was usually between 0.2 to 0.5 cc of a 0.5 per cent solution of T-1824. The exact amount of dye was injected through a polyethylene catheter by means of a syringe which had been calibrated to deliver without flushing. The umbilical vein was chosen for injection because peripheral injection through a needle is difficult in newborn infants and cannot be done under the ideal basal conditions of sleep. Immediately before the actual injection of dye blood was aspirated through the catheter to make certain that the catheter tip was in a position where blood was circulating freely. It was soon realized, however, that the anatomical position of the catheter tip and therefore of the injection site varied in different infants. In some instances the catheter could be advanced without meeting resistance, but in others obstruction was quickly met and it was necessary to maneuver the tip to get a free flow of blood. This variability in the position of the catheter is well shown on films of the abdomen of two newborn infants with radio-opaque catheters introduced through the umbilical vein (figs. 1 and 2). The significance of this will be discussed later.

Cardiac output was determined by a modification of the method described by Nicholson and Wood,⁶ using ear oximeter dye curves and calculating the output from the Hamilton equation,

\[ \text{Cardiac output} = \frac{60I}{CT} \]

where \( I \) represents the amount of dye injected in milligrams; \( T \), the duration of the primary curve in seconds; and \( C \), the mean concentration of dye during its initial passage through the ear in milligrams per liter of whole blood. The ear oximeter curves were calibrated by these authors by adding known quantities of T-1824 to arterial blood samples or to venous samples arterialized in a tonometer which were then drawn through a cuvette oximeter to

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record the corresponding deflection. Measurements of dye curves were made with a planimeter. To avoid the drawing of relatively large amounts of blood from small infants, the calibration of ear oximeter curves was modified.

Two 5-cc. samples of blood were withdrawn from a peripheral vein (from the umbilical vein in newborn infants) one before and one five minutes after intravenous injection of a calculated amount of T-1824. It was assumed that mixing of the injected dye with the circulating blood volume was completed in five minutes. The time of each withdrawal was marked on the moving chart paper of the recorder. Blood samples were centrifuged for 30 minutes at 3000 revolutions per minute. The plasma was withdrawn and the dye concentration of the five-minute sample determined in a Coleman spectrophotometer by comparison with a sample of dye-free plasma to which a known amount of dye had been added. Hematocrit values were obtained simultaneously by the Wintrobe method. These were used to calculate the dye concentration in whole blood. The relation between the dye concentration of the blood sample so determined and the deflection of the ear oximeter at the moment the blood sample was drawn was used to determine dye concentrations at other points on the dilution curve. This method removes the need for using arterial or arterialized blood for calibration. In a small group of children both venous and arterial blood samples were withdrawn simultaneously and used for quantitation of dye curves in this manner. In all instances the results were identical, and, therefore, it was considered satisfactory to use venous samples only in the study of newborn infants. Unfortunately it was not possible to check the accuracy of this modified dye dilution method against results by other methods because accepted methods for cardiac output determination are not suitable for use in healthy infants and children.

One difficulty was encountered, which may influence the accuracy of the results. This was a change in the IR reading of the galvanometer which occurred after injection of T-1824. Readjustment of the IR setting to its preinjection level resulted in a decrease in the distance between the recorded oximeter deflection and the original baseline in every instance. Two explanations for the change in IR reading may be advanced. Although the mechanical baseline appeared to be stable before the dye was injected, it is possible that it may have drifted downward gradually during the five-minute interval before the calibration sample was drawn. Since this would be a gradual change, it would not affect appreciably the depth of the curve recorded during the primary circulation and could be corrected for in the calibration sample by resetting the IR reading before drawing the blood. The other explanation assumes a direct effect of the dye on the hemoconcentration of the blood. Some foundation for this assumption lies in the fact that hematocrit values of blood withdrawn five minutes after injection of the dye were consistently lower (1 to 1.2 percentage
points) than of the preinjection sample from the same patient. Such a decrease in hematocrit values might be expected to increase the infrared light transmission of the oximeter. Other authors have noted increases in infrared light transmission following injection of T-1824, but in their cases this was associated with increased hematocrit values measured at the peak of the dye curve. They were unable to explain the increased IR light transmission to their satisfaction. Whatever the correct explanation may be, experience in our laboratory showed that impossible values of cardiac output were obtained if the IR setting was not readjusted. Consequently it was decided to readjust this setting before drawing the calibration samples.

Cardiac index was determined by dividing cardiac output by surface area. The Du Bois formula,

\[ A = H^{0.725} \times W^{0.425} \times 71.84 \]

was used. \( A \) represents the surface area in square centimeters, \( H \), the height in centimeters and \( W \), the weight in kilograms. As a matter of interest we have compared the results calculated by the method described above with those calculated by the empirical triangle method of Warner and Wood.

The mean values for cardiac output as calculated by the two methods were not significantly different. However the standard deviation of the percentage differences between results by the two methods was 17.7 per cent in a group of seven healthy children and 35 per cent in a group of 10 healthy newborn infants.

**Results**

The most remarkable finding was the lack of uniformity of contour of the dye dilution curves obtained in the group of 29 healthy infants during the first 26 hours of life. Since all infants were studied under the same basal conditions, this variation in the curves must have been related to changing circulatory patterns during the first few hours of life. Upon plotting these curves on semilogarithmic paper it becomes obvious that there are three general types of dye dilution curves in the newborn, (1) normal, (2) left-to-right shunt, and (3) diphasic (figs. 3 and 4).

1. **Normal Curves.** Ten infants had normal curves. Four of these infants were under 15 hours of age. Normal curves were characterized by the same smooth outline as curves found in healthy individuals of any age, usually with a somewhat more rapid downward than upward deflection. The length of the appearance time, build up time and disappearance time varied little within this group, with average values of 3.22, 4.9 and 7.99 seconds respectively and seemed within the expected range for the age. The mean ratio between the disappearance time and build up time (DT/BT) was 1.66. In a few instances the appearance time seemed extremely short (1.55, 1.6, 2.3 seconds). Generally speaking curves in this group appeared unexpectedly large. The average peak height was 33.8 mm., corresponding to a mean peak concentration of 14.73 mg. per liter of blood. Because the amount of dye injected per kilogram of body weight varied somewhat in different infants, peak height values were corrected on the basis of an assumed injected amount of 0.4 mg. of T-1824 per kilogram of body weight. The average corrected peak
Fig. 4. The same curves as shown in figure 3 plotted on semilogarithmic paper. The differences in contour between the various dye dilution curves are clearly seen. Primary curves are represented by solid lines, recirculation curves by broken lines.

The height was 33.0 mm. and the corrected peak concentration 14.9 mg. per liter. Since the size of a dilution curve depends largely on the amount of dye injected it is probable that in some infants the amount injected was too large. However, smaller quantities of T-1824 could not be used since in infants with left-to-right shunts the curves were rather small and shallow with the amounts used and it is not possible to anticipate the type of curve which will be obtained. Another factor which is known to influence the size of the curve is the site of injection, central injections giving rise to curves of greater height than peripheral injections. Since the injection site was not uniform because of the varying position of the catheter tip after it was introduced into the umbilical vein, the question arose whether dye could have been injected through a patent ductus venosus. This would represent a more direct pathway to the heart than if dye were injected into one of the branches of the umbilical vein or the portal vein with the ductus venosus closed. It seems unlikely that the ductus venosus was patent in all infants with normal curves particularly since normal curves occurred with greater frequency in the older infants where one might expect the ductus venosus closed more frequently. The contour of the normal curves was broader and shallower in infants with a lower cardiac output and narrower, more peaked in those with higher output. This is similar to findings in older individuals.

2. Left-to-Right Shunt Curves. Twelve infants studied had dilution curves resembling curves
associated with left-to-right shunts. All of these infants were under 15 hours of age. Curves in this group were rather shallow and more prolonged than in the group with normal curves and the time components were generally longer while concentration components were smaller. The main characteristic was a markedly prolonged disappearance time. The mean values for appearance time, build up time and disappearance time were 5, 5.3 and 17.4 seconds, respectively. The mean disappearance time–build up time ratio was 3.2, peak heights averaged 11.75 mm. and corrected peak heights 9.05 mm. Peak concentrations which were calculated only in five infants of this group had a mean value of 6.65 mg. per liter, with a corrected mean value of 6.4 mg. per liter.

Broadbent, Clagett, Burchell and Wood pointed out that an inverse correlation exists between the peak concentration and the magnitude of the A-V shunt, while a direct correlation is found between the disappearance time–build up time ratio and the size of the shunt. In order to estimate the size of the shunt the average peak concentration and disappearance time–build up time ratio were compared with values found in a group of 13 children (1 to 13 years) with interventricular and interatrial septal defects and with those from a group of six children (1½ to 15 years) with patent ductus arteriosus (table 1). It appears that the amount of blood shunted in newborns was in most instances moderately large.

### Diphasic Curves
In seven infants, varying in age between 6 and 24 hours, peculiar diphasic curves were obtained. These were characterized by a small primary curve and a rather deep recirculation curve. The primary curve had either a normal contour or the contour characteristic of a left-to-right shunt. The recirculation curve had a greatly prolonged downstroke and the upstroke in most cases was barely visible and fused indiscernibly with the final recorded line which follows injection of dye. The average values for the components of the primary curve were as follows: appearance time 4.1 seconds, build-up time 4.18, disappearance time 9.38 seconds, disappearance time–build up time ratio 2.26, peak height 12.54 and corrected peak height 9.62 mm. The recirculation time, which is the distance between the peaks of the primary and recirculation curves and corresponds to the mean ear to ear circulation time, differed in

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**Table 1.** Comparison of Time Components and Peak Heights of Evans-blue Dye (T-1824) Dilution Curves From Healthy Newborn Infants with a Central Left-to-Right Shunt Due to Atrial Septal Defect, Ventricular Septal Defect and Patent Ductus Arteriosus. Diagnosis of All Cardiac Lesions Was Confirmed by Cardiac Catheterization

<table>
<thead>
<tr>
<th></th>
<th>1-19 Years</th>
<th>Newborn (2:45–26:47 hours)</th>
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<tr>
<td></td>
<td>Normal</td>
<td>Interventricular and atrial septal defects</td>
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<td>Number of Cases</td>
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<td>Appearance time (seconds)</td>
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<td>18</td>
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<td></td>
<td>range</td>
<td>4–12.4</td>
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<td></td>
<td>S.D.</td>
<td>±2.021</td>
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<td>Build-Up time (seconds)</td>
<td>mean</td>
<td>7.66</td>
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<td></td>
<td>range</td>
<td>2.8–7.6</td>
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<td></td>
<td>S.D.</td>
<td>±1.421</td>
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<tr>
<td>Disappearance time (seconds)</td>
<td>mean</td>
<td>2.1–11.9</td>
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<td></td>
<td>range</td>
<td>1.2–11.9</td>
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<td>S.D.</td>
<td>±2.785</td>
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<tr>
<td>Ratio, Disappearance T.</td>
<td>mean</td>
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<tr>
<td>Build-up Time</td>
<td>range</td>
<td>0.68–1.8</td>
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<td></td>
<td>S.D.</td>
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<tr>
<td>Peak height of dye curve</td>
<td>mean</td>
<td>33.15</td>
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<tr>
<td>corrected to 0.4 mg./Kg. (mm)</td>
<td>range</td>
<td>16.2–62.8</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>±11.61</td>
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![Diagrams of time components and peak heights of normal and abnormal dye dilution curves in the newborn.](http://circ.ahajournals.org/)

**Fig. 5.** Comparison of time components and peak heights of normal and abnormal dye dilution curves in the newborn. The abnormal curves are either diphasic (type 1) or of the left-to-right shunt type (type 2).

**Fig. 6.** Age distribution of normal and abnormal dye dilution curves in the newborn. Abnormal curves are subdivided into types 1 and 2, diphasic and left-to-right shunt types, respectively. Values of cardiac output and cardiac index calculated from normal and abnormal dye dilution curves. The majority of those calculated from abnormal curves is outside the physiological range.

every infant (13.9, 24.9, 18.8, 30.2, 24.4 seconds; in two infants it was impossible to measure). Plotting these curves on semilogarithmic paper showed particularly well the difference in peak heights between the primary and recirculation curves. The impression gained from these curves was that only part of the injected dye reached the ear on its first circulation, which would explain the rather small primary curve, while the remainder of the dye showed up later. The reason for this delay in appearance of dye is difficult to explain. It is conceivable that there was some peripheral pooling of dye in the liver, although prior to injection of dye we always made sure by aspiration of blood that the catheter tip was in a position where blood was flowing freely. It may have been due to an artefact caused by some mechanical defect in the recording which cannot be accounted for. Finally, it is quite possible that these diphasic curves represent a right-to-left shunt through a patent ductus arteriosus. Since pressure differences between the pulmonary artery and the aorta are assumed to be small during the first few days of life, the pulmonary artery pressure might at times exceed the aortic pressure and give rise to a right-to-left shunt through a still patent ductus arteriosus. In that case part of the injected dye would not reach the ear on its first circulation but would flow through the ductus distally and would appear at the ear only after more thorough mixing had occurred.

4. Cardiac Output. The cardiac output and cardiac index were calculated in 10 infants with normal dye dilution curves. The average value for cardiac output was 547.7 cu. mm. per minute with a range from 186 cc to 854 cc. Cardiac index values varied between 0.9 and 3.7 with an average of 2.5. Infants younger than 15 hours tended to have a lower output than older infants (figs. 5 and 6). Various authors in the past have estimated the cardiac output of newborn infants on the basis of a number of theoretical considerations and arrived at values between 440 cc and 520 cc per minute.11, 12, 13, 14 These figures are similar to those of the present study. For comparison the cardiac output in five newborn infants with abnormal curves suggesting a left-to-right shunt and in four infants with diphasic curves were calculated. The average cardiac output and cardiac index in the first group was 1341 cc per minute (range 934 to 2050) and 6.36 (range 4.1 to 10.5), respectively. In the second group the mean cardiac output was 1244 cc per minute (range 343 to 2320) and cardiac index 5.93 (range 1.8 to 14.4). As one might expect, values in both groups were excessively high and outside the physiological range.

**DISCUSSION**

It seems necessary to find a plausible explanation for the occurrence of abnormal types of curves in normal newborn infants.
Most likely they are due to some fetal channel not yet closed, particularly since the incidence of these curves diminishes in infants older than 15 hours. It is generally thought that with the onset of breathing pulmonary resistance decreases, thereby permitting a larger amount of blood to reach the lungs. The increased amount of blood which returns from the lungs raises the left atrial pressure and thereby closes the valve guarding the foramen ovale. The foramen ovale then remains physiologically closed, anatomical closure following later. The mechanism of closure of both the ductus arteriosus and ductus venosus is incompletely understood. The exact time of physiological closure of any of the fetal pathways has not been proven in the human newborn, although a great deal of information has been gained from the work of Barclay, Barcroft and others who studied the closure of these channels in animals, particularly in lambs (15, 16). Their findings are, however, not necessarily applicable to the human infant. The effect of the persistence of any of the three fetal channels, foramen ovale, ductus arteriosus, or ductus venosus, upon the size or shape of the dye dilution curve can best be discussed by considering separately each type of curve found in this group of newborn infants. Curves with normal contour are of rather large size and in three of these curves the appearance times seem excessively short: 1.5, 1.6, and 2.3 seconds. The reason for this is not easily explained. It is conceivable that in these three infants the circulation rate was very fast, due to a rapid heart rate, thus causing the injected dye to appear at the ear oximeter site more rapidly. Evidence for this is not available since heart rates were not recorded simultaneously with the dye injections. Another possible explanation for the very short appearance time is that T-1824 was injected through a patent ductus venosus, reaching the inferior vena cava directly instead of having to pass through the capillary bed of the liver before reaching the right atrium. An attempt to determine the patency of the ductus venosus was made by introducing a radio-opaque catheter through the umbilical vein and taking x-ray pictures in two infants. In one infant the catheter passed into a mesenteric vein and in the other it was located in the liver, but the ductus venosus was not entered. This study, therefore, offers no positive evidence that the ductus venosus does not close immediately after birth, although it does not exclude that possibility. The question arose whether the very short appearance times could have been caused by a right-to-left shunt through the foramen ovale. We think this unlikely since the curves in question had a smooth outline without the usual double hump on the downstroke found in the presence of right-to-left shunts. A smooth curve could result under these circumstances only if the catheter tip were located right at the opening of the foramen ovale and all dye were injected into the left atrium. It is extremely doubtful that the catheter tip reached this position. The fact that a double hump curve has not been observed in the present study argues against the presence of right-to-left shunts in the newborn infant under the conditions of the test, i.e. with the infant asleep. Lind and Wegelius,17 who studied the circulation in newborn infants by angiocardiography, were able to show the presence of small right-to-left shunts through the foramen ovale during the first six days of life. Prec and Cassels18 also found good evidence for such shunts while studying changes in arterial oxygen saturation in newborn infants during crying. The most probable reason why such a shunt was not demonstrated in the present study was that infants were studied while asleep. Under these conditions it is less likely that blood is shunted from the right to the left atrium through the foramen ovale since the right atrial pressures tend to be lower than the left atrial pressures. During crying this normal pressure relationship is frequently reversed and can lead to a right-to-left shunt during the early newborn period when the foramen ovale is not anatomically closed. It seems possible that infants studied by Lind and Wegelius were either crying during the angiocardiography or else that the normal atrial pressure gradient was reversed by injection of a relatively large amount of contrast material into the right atrium.

The most interesting finding in our present
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study was the occurrence of left-to-right shunt curves in a number of newborn infants under 15 hours of age. The injection site seems to be unimportant in the production of these curves. Since a left-to-right shunt curve was also obtained after injection of dye into the antecubital vein of a newborn infant 4 hours 8 minutes old (fig. 7). A patent ductus venosus could hardly give rise to this particular type of curve nor is it likely that a left-to-right shunt could occur through a patent foramen ovale. The latter opening is guarded by a valve which closes at birth due to increased filling pressure in the left atrium. Because of the anatomical position of this valve it seems improbable that an appreciable amount of blood could be shunted from the left into the right atrium through the foramen ovale as long as this valve is intact. By exclusion our evidence favours the presence of a patent ductus arteriosus through which a left-to-right shunt could occur as soon as the aortic pressure exceeds the pulmonary artery pressure. The average systemic blood pressure at birth measured in the umbilical arteries is about 80/46 mm. Hg, and the systolic pressure increases within the first 24 hours by about 10 mm. and by another 10 mm. within the next 10 days. At birth pulmonary artery pressures and aortic pressures are assumed to be equal, but how long it takes for the aortic pressure to exceed the pulmonary pressure is not known. The assumption of a left-to-right shunt under suitable pressures presupposes the patency of the ductus arteriosus. It is not known definitely how long the ductus arteriosus remains open in the human newborn. In the fetal sheep functional closure of the ductus has been observed within five minutes after birth. However more recently Dawes, Milne, Mott and Widdicombe observed blood flows from the aorta into the pulmonary trunk in the newborn lamb which apparently lasted for several hours after delivery. They also observed closing of the valve of the foramen ovale within one to two minutes after the onset of breathing. These authors used cineangiography following injection of 70 per cent Thorotrast into the aortic arch. From our findings it seems very likely that the ductus arteriosus remains open also in newborn infants for varying periods after birth. The exact time of closure probably varies in different infants, but we have not found left-to-right shunt curves in infants older than 15 hours. Whether a reversal of shunt through the ductus arteriosus can occur in some infants under conditions of a higher pulmonary artery than aortic pressure cannot be stated with certainty. The peculiar diphasic curves found in some infants both younger and older than 15 hours could be the result of a right-to-left shunt through the ductus arteriosus. Eldridge, Hultgren and Wigmore measured the oxygen content and capacity of capillary blood samples obtained from the previously warmed right hand and foot of 27 normal newborn infants during the first five days of life. The Roughton-Scholander microtechnic was used. They found that 9 of 11 infants 1 to 3 hours old had a significantly lower oxygen saturation in the foot than in the hand. In infants between 3 and 72 hours of age 5 of 10 cases showed a similar difference in oxygen saturation, but in those older than 3 days no difference was observed. They explained these findings on the basis of a venoarterial shunt through a patent ductus arteriosus. These observations support the view that the diphasic curves probably represent a right-to-left shunt through the ductus arteriosus. More study with better methods is needed to determine more accurately the time of closure of the various fetal pathways.

In regard to cardiac output and cardiac index, the modified dye dilution method is relatively easy to use in small infants and the results obtained seem fairly accurate. This method has made it possible for the first time to measure the cardiac output of healthy newborn infants.

Conclusions

Newborn infants over 15 hours of age have a tendency to show dye dilution curves of
normal contour following the injection of a measured amount of T-1824 dye into the umbilical vein. Below this age a large percentage of infants have curves of abnormal contour, generally one of two types: either a left-to-right shunt type or a diphasic type. The most likely explanation for the former is a left-to-right shunt through the ductus arteriosus which has not yet closed. The latter type may be explained by a shunt reversal through the ductus arteriosus. Patency of the foramen ovale apparently is not concerned in the production of abnormal dye curves in the newborn infant under conditions of sleep.

Cardiac output has been satisfactorily determined by a modified dye dilution method which has been discussed in detail. The mean cardiac output value of 540 cc. per minute comes close to values estimated by a number of investigators on the basis of theoretical considerations.

SUMMARIO IN INTERLINGUA

Le curvas del dilution de colorantes e le rendimento cardiac esseva studiate in 29 neonatos de bon sanitate durante le prime 26 horas de lor vita. Esseva usate le metodo de Wood e socios. Trenta-sex pro cento del infants studiate habeva curvas de contorno normal. In le majoritate de iste casos le infants esseva plus que 15 horas de etate. Infra le etate de 15 horas le infants tendeva a haber curvas de forma anormal. Isto esseva o diphasic o resimilava curvas del tipo associate con derivation ab le sinistra verso le dextera. Il es probable que illos esseva causate per un patente ducto arterioso. Le rendimento cardiac median esseva 540 cc per minuta.

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REFERENCES


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