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REVIEW ARTICLE

Tailor-made circulatory management based on the stress–velocity relationship in preterm infants

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Preterm infants frequently experience pulmonary hemorrhage or cerebral intraventricular hemorrhage after birth. The immature myocardium of the left ventricle faces a high afterload after the baby is separated from the placenta. However, the preterm left ventricle has limited ability to respond to such an increase in afterload. This results in depressed cardiac function and a deterioration in hemodynamics. We speculated that the perinatal deterioration in cardiac performance would be closely related to serious hemorrhages. To prove our hypothesis, we studied the interrelationship between the perinatal changes in cardiac performance and the incidences of intraventricular and pulmonary hemorrhage. We obtained the stress–velocity relationship (rate-corrected mean fiber shortening velocity and end-systolic wall stress relationship) by M-mode echocardiography and arterial blood pressure measurement. We found that the incidences of intraventricular and/or pulmonary hemorrhages were higher in infants with an excessive afterload, which resulted in a decrease in the function of the left ventricle. We suggest that careful attention to keep the afterload at an acceptable level by vasodilator therapy and sedation may reduce or prevent these serious complications. In this review, we will discuss our data along with related literature.

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Introduction

Preterm infants occasionally experience heart failure after birth. This is usually treated by an intravenous infusion of catecholamines such as dopamine and dobutamine. Some of these infants may experience serious hemorrhagic complications such as pulmonary hemorrhage or cerebral intraventricular hemorrhage (IVH), which usually occur within 72 hours after birth.

It is well known that the perinatal transition from the fetal to the postnatal circulation causes dramatic loading changes on the heart. This causes a significant hemodynamic stress on the cardiovascular system, especially in preterm infants with premature myocardial function. The major cause of the hemodynamic stress is the interruption of the placental circulation at birth. Because the placenta has the lowest vascular resistance of all human organs, the sudden interruption of the placental circulation results in an abrupt increase in resistance in the systemic arteries, and thus in an increase in the afterload on the left ventricle of the heart.[1–4] In addition, the left ventricle may also face increased preload from a left-to-right shunt caused by a symptomatic patent ductus arteriosus (PDA).[5,6] The immature myocardium in premature infants has limited ability to respond to an increased afterload and a change in preload.

In this paper, we discuss our clinical impression that the perinatal changes in cardiac performance are closely related to serious hemorrhage in preterm infants, and we speculate on the usefulness of catecholamine treatment to reduce or prevent such serious complications. We aimed to clarify the serial changes in left ventricular (LV) afterload in relation to pump function in premature infants in a clinical setting, and how these data relate to pulmonary hemorrhage or cerebral IVH.[7–10]

Cardiac function evaluated by the stress–velocity relationship

The LV ejection fraction (EF) and fractional shortening (FS) are commonly used to estimate LV systolic function, although EF and FS are largely influenced by preload, afterload, and heart rate.[11] Thus, these load-dependent indices cannot be reliably used to evaluate cardiac function in the unstable circulation of infants shortly after birth. Instead, an index called the stress–velocity relationship[11] has been used clinically for ill infants as a sensitive and relatively load-independent index.[2–4,11–16] This index is calculated from the end-systolic wall stress (ESWS), which is an index of LV afterload, and the LV rate-corrected mean velocity of circumferential fiber shortening (mVcfc), which is an index of LV pump function. ESWS is calculated from blood pressure and LV dimensions by echocardiographic measurement,[11,12] and mVcfc is calculated from the LV FS, ejection time, and heart rate (Fig. 1).[11]

The stress–velocity relationship showed a steep slope in the low ESWS range, as seen in Fig. 2. This has also been shown by others.[2–4,11–16] Our own data and data from others indicate that the ESWS or afterload is lower in younger age groups than in older age groups. Therefore, the cardiac pumping function is easily impaired and mVcfc is easily decreased by even a small increase in afterload or ESWS in smaller or younger infants with low ESWS.[3,15,16] All previous reports on the stress–velocity relationship relate to preterm infants who were not treated with circulatory agonists,[2,3,17] and there have been no reports on the changes in these parameters in preterm infants treated with catecholamines.

A geometric requirement for measuring ESWS is a cross-sectional view of a left ventricle that is almost circular.

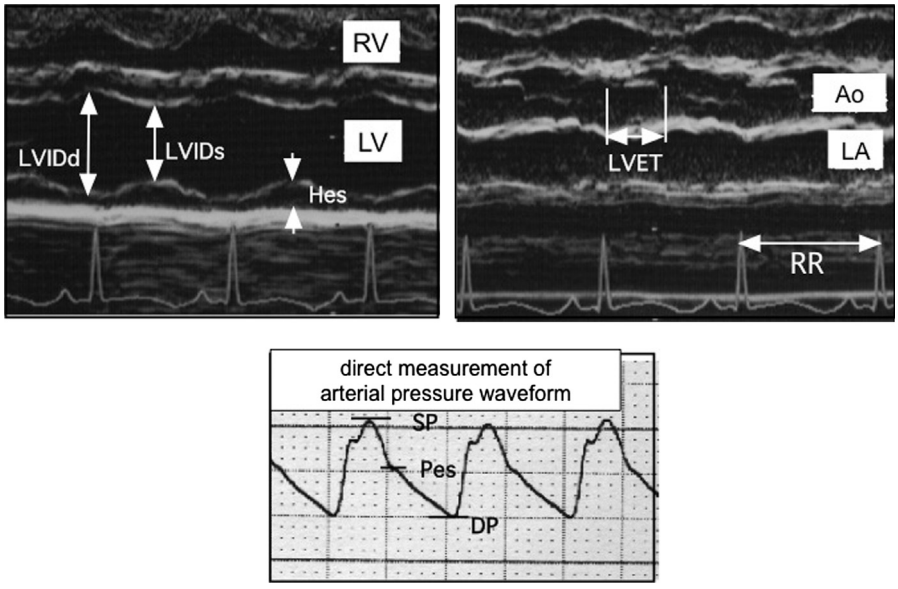

Figure 1 Methods for estimation of mVcfc and ESWS.[7] mVcfc (circ/s) = {(LVIDd LVIDs)/LVIDd} × $RR^{1/2}$/ET; ESWS (g/cm^2) = 1.35 X LVIDs × Pes /{4XHes(1 + Hes/LVIDs)}. LVIDd = left ventricular internal dimension-diastole; LVIDs = left ventricular internal dimension-systole; Pes = end-systolic pressure; Hes = posterior wall thickness at end-systole; ET = left ventricular ejection time; RR = RR interval; SP = systolic pressure; DP = diastolic pressure. Pes was measured by assigning the systolic pressure to the peak of the trace and the diastolic pressure to the low point of the trace, with subsequent linear interpolation to the level of the dicrotic notch.

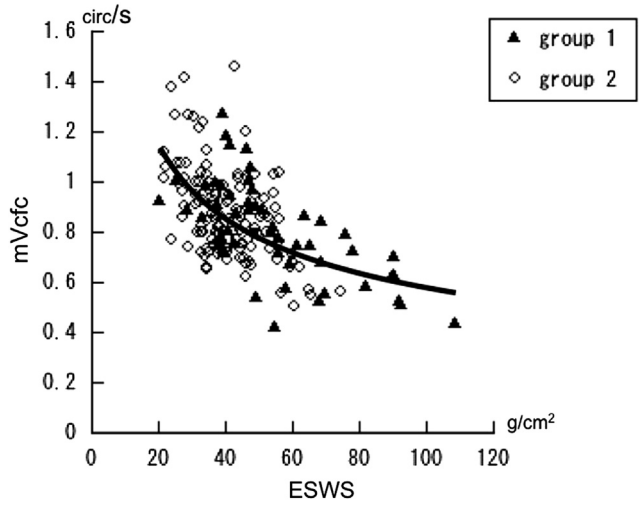

Figure 2 Stress—velocity relationship (mVcfc-ESWS relationship).[7] There were significant correlations between ESWS and mVcfc in both groups ($mVcfc = 3.76 \times ESWS^{-0.4}$; $p < 0.01$, $R = 0.56$). Group 1: infants with complications (pulmonary hemorrhage, intraventricular hemorrhage, and periventricular leukomalacia; $n = 9$). Group 2: infants without complications ($n = 24$). Systolic blood pressure (sBP) and mean blood pressure (mBP) changed over time, with no differences between the groups.

However, this is difficult to achieve in the early days after birth because of physiologic pulmonary hypertension, which distorts LV shape by flattening the interventricular septum. Katayama assessed ESWS in patients with congenital heart disease in which the cardiac interventricular septum was flattened by increased right ventricular (RV) pressure.[18] Katayama concluded that the stress—velocity relationship could be applied to cases with increased RV pressure, even at RV pressures as high as the LV pressure.

There is also concern about the influence of PDA on the usefulness of the stress—velocity relationship. However, it has been reported that mVcfc and ESWS do not change after PDA closure,[4,17] which indicates that a PDA does not affect the measurement of these parameters. Thus, the stress—velocity relationship is considered to be a useful index for evaluating cardiac function in preterm infants in their early days of life.

Since 2000, we have performed circulatory management in preterm infants based on the cardiac function evaluated by the stress—velocity relationship.[7–10] Here we present the usefulness of our method for improving the treatment outcomes of preterm infants.

Serial echocardiographic assessment of the stress—velocity relationship in preterm infants with perinatal complications

We previously reported that cardiac dysfunction due to increased afterload is associated with pulmonary hemorrhage and/or IVH in preterm infants.[7] We prospectively studied the serial changes in the ESWS—mVcfc relationship during the first 60 hours of life in 33 preterm infants born at 24—31 weeks of gestation in Kanagawa Children's Medical Center. The infants were divided into two groups based on perinatal complications such as pulmonary hemorrhage, IVH, and/or periventricular leukomalacia. The infants in Group 1 ($n = 9$) had complications, whereas the infants in Group 2 ($n = 24$) did not have any of these complications.

Systolic blood pressure and mean blood pressure changed over time, with no differences between the two groups (Fig. 3).[7] ESWS started to increase at 6 hours after birth, and was significantly higher in Group 1 than in Group 2 from 24 hours (up to 60 hours after birth) (Fig. 4).

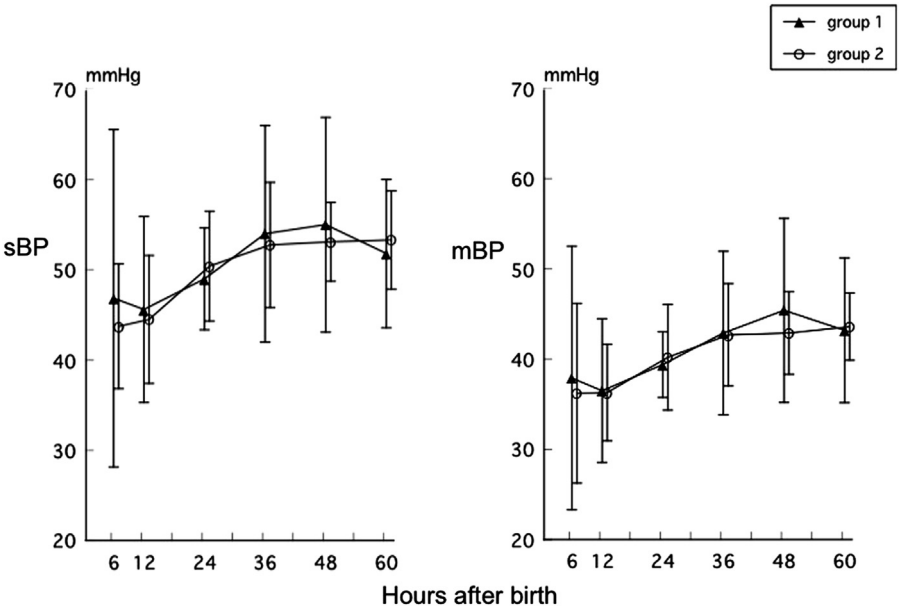

Figure 3 Serial changes in blood pressure. Group 1: infants with complications (pulmonary hemorrhage, intraventricular hemorrhage, and periventricular leukomalacia; $n = 9$). Group 2: infants without complications ($n = 24$). Systolic blood pressure (sBP) and mean blood pressure (mBP) changed over time, with no differences between the groups.[7]

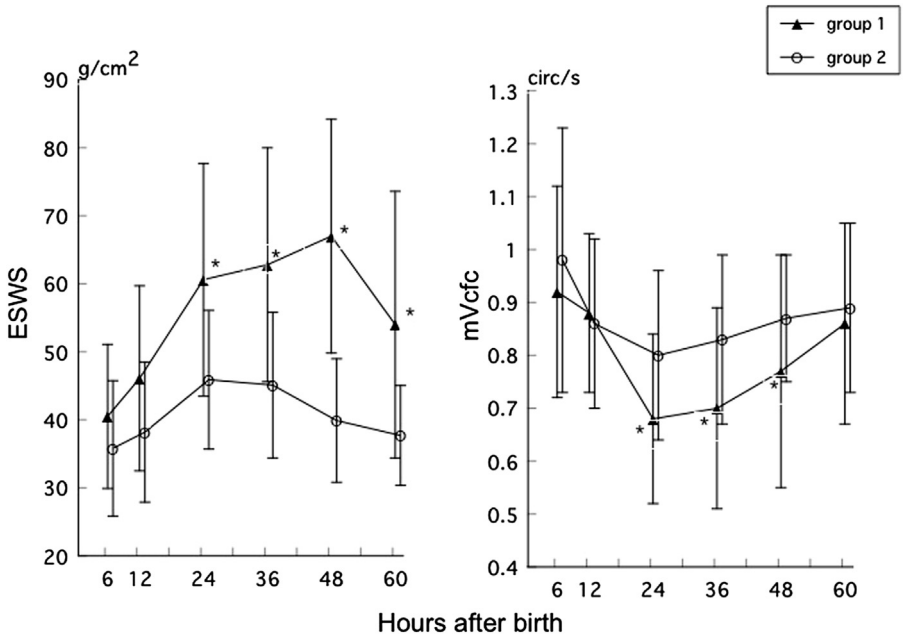

Figure 4 Serial changes in ESWS and mVcfc. The changes over time in ESWS differed significantly between the groups with a peak occurring at 24 hours.[7] The infants with complications had significantly higher ESWS values than the infants without complications at 24, 36, 48, and 60 hours after birth. The mVcfc changed over time in both groups, with a nadir occurring at 24 hours and the values in group 1 being significantly lower than those in group 2 at 24, 36 and 48 hours after birth. Group 1: infants with complications (pulmonary hemorrhage, intraventricular hemorrhage, and periventricular leukomalacia; $n = 9$). Group 2: infants without complications ($n = 24$).

The changes in mVcfc were opposite to the changes in ESWS, the nadir of mVcfc occurring at 24 hours in both groups (Fig. 4).[7] The mVcfc in Group 1 was significantly lower than that in Group 2 at 24 hours, 36 hours, and 48 hours after birth. There were significant correlations between ESWS and mVcfc in both groups ($mVcfc = 3.76 \times ESWS^{-0.4}$; $p < 0.01$, $R = 0.56$) (Fig. 2).[7] As previously stated, this indicates that the LV pump function of the preterm infant can easily be suppressed by a subtle increase in afterload, thus causing reduced cardiac output. We speculate that LV pump dysfunction due to an excessive afterload, as presented by the stress—velocity relationship, somehow induces pulmonary or intraventricular hemorrhage.

Mechanism of afterload mismatch in preterm infants

An increase in systemic vascular resistance or LV afterload suppresses cardiac pump function and decreases cardiac output. This is normally compensated for by preload recruitment to maintain the output, which is called preload reserve. In the case of an excessive increase in afterload, preload recruitment may not be enough to maintain cardiac output. This is defined in the field of cardiology as afterload mismatch. The fetal circulation is a parallel circulation with both ventricles pumping blood to the body. Stroke volume, and therefore output, is lower in the left ventricle than in the right ventricle at the fetal stage.[19] After birth, the LV preload increases as the circulation changes from parallel to serial because of the establishment of the pulmonary circulation: the right ventricle pumps blood to the lungs and the left ventricle pumps blood to the body.[15] In addition, LV afterload increases after the connection to the placenta is severed, as described above.

Afterload mismatch occurs when there is insufficient preload recruitment or venous return to compensate for the excessive afterload, or when the limit of the Frank—Starling curve (the limit of the preload reserve) has been reached. Around 24 hours after birth, the pulmonary vascular resistance decreases and the shunt flow through the ductus arteriosus increases. Accordingly, the preload increases rapidly. However, the left ventricle of the preterm infant is known to have low distensibility.[1,20] Therefore, preterm hearts cannot accept large volumes of blood, which results in an increase in pulmonary venous pressure and venous congestion. In these cases, pulmonary congestion may occur even when the left ventricle is exposed to a relatively small increase in preload, indicating that the preload reserve is limited in the preterm infant. In this condition, the left ventricle will be functionally depressed when faced with a large increase in afterload because of a low capacity for preload recruitment (limited preload reserve).

Myocardial hypertrophy is one of the mechanisms to compensate for the overload of the heart. However, this is a chronic mechanism and has a limited effect in the early days after birth. Therefore, an increase in preload and afterload results in ventricular dilatation. This dilatation then results in an increase in systolic ventricular wall stress, which in turn reduces myocardial shortening and ventricular pump function, leading to a further decrease in cardiac output. The depressed cardiac output then further increases the need for preload recruitment, which ultimately worsens pulmonary congestion.

As it is known that the diastolic and systolic functions are immature in the premature heart compared with the mature heart,[20] we speculated that the premature heart cannot respond to the increased preload and afterload shortly after birth, and is thus susceptible to afterload mismatch during the serial changes in blood pressure after birth.[7]

Relationship between afterload mismatch and IVH

The subependymal germinal matrix, which is the most common site of IVH, increases in volume until about 26 weeks of gestation.[21,22] It is a fetus-specific component that begins to decrease at 26 weeks of gestation and disappears around 34 weeks of gestation.[21,22] The vein in the subependymal germinal matrix has poor supporting tissues and a thin vascular wall, both of which make it susceptible to bleeding when the venous pressure increases.[21,22] When bleeding occurs at the subependymal germinal matrix, periventricular veins will be occluded, and this congestion may extend to the periventricular parenchyma, causing periventricular hemorrhage.[23]

The left and right ventricles of the heart interact closely with each other, which is called ventricular interaction. For example, RV diastolic pressure increases after LV dilatation, even if there is no change in RV diastolic function or RV myocardial characteristics. This interaction is most prominent in the premature heart compared with the mature heart.[20]

Our data showed that LV ESWS or LV afterload was higher in infants with serious hemorrhagic complications. As discussed above, to cope with an increase in afterload, preload to the heart is increased because of the preload reserve. The increase in LV preload is manifested by an increase in pulmonary venous pressure, which may lead to pulmonary hemorrhage. Because of the tight ventricular interaction early after birth, the change in LV loading conditions should be paralleled by the right ventricle. Thus, an increase in LV preload is very likely associated with an increase in RV preload or an increase in central venous pressure, which impede the systemic venous return and lead to an increase in the cerebral venous pressure. Then, finally, the fragile vein in the subependymal germinal matrix cannot tolerate the elevated intracardiac venous pressure, leading to bleeding and IVH.[7]

Direction of circulatory management for prevention of IVH

Central venous pressure (CVP) monitoring is not practical in the circulatory management of preterm infants. In CVP monitoring, emphasis is placed largely on blood pressure. However, an increase in cardiac preload or venous pressure because of excessive afterload cannot be predicted by blood pressure or urine volume. We have already discussed how venous congestion is associated with pulmonary hemorrhage and IVH. Thus, these hemorrhages cannot be prevented with cardiotonic therapy judged from the blood pressure data alone. Instead, the aim of circulatory management in preterm infants should be to avoid the increase in venous pressure caused by excessive afterload.

Evaluation of circulatory agonists using the stress—velocity relationship

We investigated how circulatory agonists affect excessive afterload. We evaluated the changes in the stress—velocity relationship prior to and after the use of dobutamine and a vasodilator nitroglycerin in very low birthweight infants.[24] Dobutamine, at a dose of 4 μg/kg/min, increased blood pressure in all infants. However, the stress—velocity relationship showed that the cardiac pump function improved in only half of the infants, whereas ESWS was increased and cardiac pump function deteriorated in the other half. Dobutamine did not clearly improve low mVcfc, particularly when ESWS was increased.[24] By contrast, a dose of 0.5—1.5 μg/kg/min nitroglycerin, which was used when ESWS was elevated, reduced ESWS and increased mVcfc in 17 of 19 infants.[24]

Vasodilators and PDA in preterm infants

We expected that vasodilators would improve cardiac pump dysfunction caused by excessive afterload in preterm infants. We further speculated if vasodilators would induce symptomatic PDA in preterm infants. Because there were no reports regarding this issue, we performed experiments using the whole-body rapid freezing technique in rats to see if the ductus arteriosus was kept open or was reopened after physiologic closure after birth in response to the following vasodilating agents: phosphodiesterase (PDE) 3 inhibitors such as milrinone, and a PDE5 inhibitor such as sildenafil, nitroglycerin, human antinatriuretic peptide (hANP), or magnesium sulfate.[25—28] We found that these vasodilators exerted ductus arteriosus dilating effects in a dose-dependent manner in fetal and neonatal rats, and the dilating effects of the vasodilators were approximately 10 times higher in preterm than in near-term fetal rats.[25,26]

In a clinical study, we evaluated the effects of nitroglycerin at a low dose (0.3—1.5 μg/kg/min) on PDA in preterm infants, and reported that nitroglycerin reduced afterload, even at these low doses, and did not affect the frequency and efficacy of indomethacin use.[29] The latter observation implies that nitroglycerin did not induce a clinically significant opening of the ductus. Thus, we concluded that low-dose nitroglycerin can be used without concern about its dilating effect on the ductus in clinical practice.

Circulatory management to prevent pulmonary hemorrhage and/or IVH in preterm infants based on the stress—velocity relationship

Previously, we routinely administered a volume infusion and catecholamines to preterm infants if the mean blood pressure did not reach 30 mmHg. However, since 2002, we have selected therapeutic drugs for cardiovascular support based on the stress—velocity relationship. We started to continuously monitor blood pressure from the early days after birth to monitor the systemic circulation. To prevent excessive afterload, we administered prophylactic morphine infusions (8—10 μg/kg/h) to all infants receiving mechanical ventilation, which very likely increases

ventricular afterload. Catecholamines were administered after the administration of 2–3 mg/kg hydrocortisone if the mean blood pressure did not reach the expected value for gestational age, the urine volume was not maintained, metabolic acidosis developed, or lactic acid concentrations continuously increased.

Cardiotonic therapy using catecholamines was indicated for cardiac pump dysfunction (EF <50% or mVcfc <0.8 circ/s) at ESWS <40 g/cm^2, and dobutamine was given at a dose of 2–4 μg/kg/min. Load reduction therapy was indicated in infants with cardiac pump dysfunction with ESWS ≥45 g/cm^2, or in infants with ESWS <45 g/cm^2 in whom there was a trend toward increased ESWS and decreased EF and mVcfc. In these infants, we started nitroglycerin at a dosage of 0.3 μg/kg/min and increased the dosage according to its efficacy. The initial dosage was selected because it did not show any adverse effects related to the ductus, as stated above. We called this strategy tailor-made circulatory management.

Outcomes of the tailor-made circulatory management strategy in preterm infants born at 23 weeks' or 24 weeks' gestation

In 2005, we reported the outcomes of the tailor-made circulatory management strategy based on the stress–velocity relationship, particularly focusing on the outcomes of serious hemorrhagic complications, in preterm infants born at 23 weeks or 24 weeks of gestation.[8,9]

Nineteen preterm infants born at 23 weeks' or 24 weeks' gestation (mean 23.5 weeks, body weight 630 g) were studied by echocardiography and cerebral ultrasound during the first 60 hours after birth.[8] As stated above, we administered nitroglycerin to infants with a low mVcfc and high ESWS.[8] All infants except one had no ESWS recordings of more than 50 g/cm^2 throughout their clinical course. IVH higher than Grade 3 and pulmonary hemorrhage developed in only one infant with elevated ESWS. Sixteen of the 19 babies survived to discharge. Our data strongly suggested that careful management to control excessive afterload improves morbidity and mortality in these extremely preterm infants.

We then compared the outcomes of infants who received tailor-made circulatory management with those of infants who did not.[9] We used classic circulatory management strategies until the year 2000, and we collected data from 27 infants born at 23 weeks or 24 weeks of gestation between 1995 and 2000. Their data were compared with the data from 27 infants given tailor-made circulatory management between 2002 and 2005 (Table 1). Both the rate and dose of volume infusion therapy and the rate of catecholamine administration were reduced by the new strategy. Much more important was that, after the introduction

Table 1 Clinical outcomes in extremely preterm neonates on classic circulatory management or on tailor-made circulatory management based on the stress–velocity relationship.

	Classic treatment group (n = 27)	Tailor-made treatment group (n = 27)	p value
Period	1995–2000	2000–2005	
Gestational age (weeks)	23:5 + 24:22	23:11 + 24:16	
Birth weight (g)	685 ± 91	643 ± 119	0.15
Apgar score (5 min)	6.1 ± 2.4	7.2 ± 2.5	0.11
Volume infusion therapy	10 (37%)	3 (11%)	0.02
Dobutamine (DOB)	22 (81%)	5 (19%)	<0.01
Nitroglycerine (NTG)	10 (37%)	13 (48%)	0.41
Indomethacin	12 (44%)	21 (71%)	0.01
PDA ligation (<1 week)	0 (0%)	1 (4%)	0.31
IVH (any Grade)	8 (30%)	3 (11%)	0.09
IVH (Grade 3 or 4)	6 (22%)	1 (4%)	0.04
Periventricular leucomalacia	0 (0%)	0 (0%)	
Pulmonary hemorrhage	5 (19%)	2 (7%)	0.22
PDA ligation (≥1 week)	0 (0%)	4 (15%)	0.03
IP or NEC	0 (0%)	2 (7%)	0.15
Survival discharge[a]	21 (78%)	24 (88%)	0.27
	Classic treatment group (n = 17)	Tailor-made treatment group (n = 20)	p value
Cerebral palsy	2 (11%)	1 (5%)	0.51
Epilepsy	3 (16%)	0 (0%)	0.06
DQ at 18 months	65.6 ± 22.9	76.4 ± 21.9	0.15
DQ at 3 years	69.7 ± 23.4	77.9 ± 18.8	0.23
DQ at 3 years <50	5 (29%)	2 (10%)	0.18

Data are expressed as mean ± SD or number of patients (%).
DQ = Developmental Quotient measured using the Kyoto Scale of Psychological Development; IP = intestinal perforation; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus.
[a] One patient from Group 1 died after discharge. Rates of follow-up were 85% in the Classic treatment group and 83% in the Tailor-made treatment group.

of tailor-made circulatory management, IVH was reduced both in incidence and in severity, and the survival rate improved, with a trend towards a decrease in mental retardation (Table 1).[9]

Between 2006 and 2009, 24 of 27 premature infants born at 23 weeks or 24 weeks of gestation survived, and the incidence of severe IVH (Grade 3 and Grade 4) was only 4% in our neonatal intensive care unit (NICU) (unpublished data).

In 2006, we reported the clinical outcomes of 107 extremely low birthweight infants (<1000 g at birth) who had received tailor-made circulatory management. Ninety-five percent of these infants were discharged alive, and there were no deaths within 1 week of birth. The incidence of severe IVH was reduced to 1.9%.[10]

Reports on the stress—velocity relationship from other NICUs in Japan

In Japan, there have been scattered reports on circulatory management based on the stress—velocity relationship from other medical institutions. Some reports have described that the circulatory management was effective for preventing cardiac dysfunction and perinatal complications,[30—34] whereas other reports have stated that it had no effect on the outcomes.[35,36] From these reports, it can be concluded that the short-term prognosis of the new strategy is possibly better than that of the classic circulatory management strategy with routine cardiotonic therapy. We should evaluate the merits and demerits of tailor-made circulatory management based on the stress—velocity relationship on the long-term prognosis of preterm infants.

Conclusions

Cardiac pump dysfunction with excessive afterload in preterm infants results from the immature myocardium struggling to adapt to the sudden increase in vascular resistance at birth. Excessive afterload is a risk factor for afterload mismatch.

The pump function of the left ventricle in preterm infants can easily deteriorate when faced with an acute increase in afterload during the first few days after birth. This is likely the major hemodynamic mechanism behind cerebral intraventricular or pulmonary hemorrhage.

The tailor-made circulatory management strategy based on the stress—velocity relationship is expected to reduce these serious hemorrhagic complications.

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