Effects of dobutamine on ventricular functions and cerebral blood flow in preterm infants with mild hyaline membrane disease

Sudigdo Sastroasmoro

Abstrak

Penelitian ini bertujuan untuk mengetahui status kardiovaskular pada neonatus kurang bulan (NKB) dengan penyakit membran hialin (PMH) ringan dan responsnya terhadap pemberian dobutamin. Penelitian dilakukan di RS Dr. Cipto Mangunkusumo, Jakarta, dari bulan November 1997 hingga Mei 1998. NKB dengan PMH ringan diikutsertakan dalam penelitian bila berat lahirnya >1250 gram dan usia <48 jam. Pemeriksaan dilakukan secara non-invasif dengan ekokardiografi dan/atau Doppler. Parameter fungsi diastolik ventrikel kanan (VKa), yakni puncak E dan A, serta rasio E/A, tidak berbeda bermakna antara NKB dengan atau tanpa PMH ringan, dan dobutamin tidak mengubah nilai-nilai tersebut. Sebaliknya puncak E dan A pada ventrikel kiri (VKi) berbeda bermakna antara NKB dengan dan tanpa PMH ringan, namun rasio E/A tidak berbeda. NKB dengan PMH ringan mempunyai periode pre-ejeksi (PPE) lebih panjang, dan waktu ejeksi ventrikel kiri (WEVKi) lebih pendek, dan rasio PPE/WEVKi lebih besar dibanding NKB kontrol. Gangguan faal sistolik dan diastolik VKi tersebut berkurang dengan pemberian dobutamin. Kecepatan aliran darah otak (KADO) yang diperiksa dengan teknik Doppler di a. serebri anterior menunjukkan bahwa aliran maksimal dan minimal, indeks Pourcelot, serta akselerasi aliran tidak berbeda antara NKB dengan dan tanpa PMH ringan. Pemberian dobutamin tidak mengubah KADO namun meningkatkan akselerasi ADO. Disimpulkan bahwa pada PMH ringan terjadi gangguan faal diastolik dan sistolik VKi yang dapat diperbaiki dengan pemberian dobutamin. Pada NKB dengan PMH ringan fungsi diastolik VKa tidak terganggu, demikian pula KADO tidak terganggu dan pemberian dobutamin tidak mengubah KADO namun mempercepat akselerasi aliran darah.

Abstract

This study aimed to determine cardiovascular involvement in mild hyaline membrane disease (HMD) and its response to dobutamine administration. The study was done at Dr. Cipto Mangunkusumo Hospital, Jakarta, from November 1997 to May 1998. Study subjects were preterm infants with mild HMD with the birth weight of >1250 grams, and aged less than 48 hours. All measurements were done by using non-invasive methods, i.e., echocardiography and/or Doppler technique. RV diastolic function parameters (points E and A, and E/A ratio) were not significantly different between infants with or without mild HMD, and dobutamine did not alter the values. In contrast, LV E and A points were significantly different between the two groups, although the E/A ratio was not different. Infants with mild HMD had significantly longer rate-corrected PEP, shorter rate- corrected LVET, and larger PEP/LVET ratio compared with those without HMD. The LV diastolic and systolic dysfunctions were improved by dobutamine. Cerebral blood flow velocity (CBFV) determined by Doppler at the anterior cerebral artery showed that maximal and minimal flows, Pourcelot Index, and flow acceleration were not different between infants with or without HMD. Dobutamine did not alter CBFV but increased blood flow acceleration. It is concluded that LV diastolic and systolic functions are depressed in mild HMD; and dobutamine can correct the dysfunction; however, RV diastolic function is not disturbed in mild HMD. CBFV is not altered in mild HMD; dobutamine has negligible effect on CBFV, but it increases CBF acceleration.

Keywords: *Dobutamine, preterm infants, hyaline membrane disease, cardiovascular involvement, cerebral blood flow velocity*

Hyaline membrane disease (HMD) is one of the most challenging problems in neonatal period both in developing and in industrial countries.[1] This disease is the leading cause of perinatal morbidity and mortality. Proper management of HMD requires sophisticated technology, i.e., use of mechanical ventilation with or without surfactant replacement therapy. In most developing countries the two modalities are not available for the majority of patients because of problems with facility and cost. Consequently, many of those babies are left untreated and eventually die. HMD is caused by deficiency of surfactant, a surface active agent that prevents the alveoli from atelectasis. Surfactant is synthesized by type II pneumocytes, starting at 22 weeks gestational age and reaching its optimal amount at term.

Department of Child Health, Faculty of Medicine, University of Indonesia/Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

One of the complications of HMD is its effects on the cardiovascular system. In severe HMD the cardiac functions are disturbed;[2,3] however, in mild form of HMD this has not been elucidated. (In this study, mild HMD is defined as HMD that does not require mechanical ventilation). Similarly, dobutamine, a titrable inotropic agent which is known to improve cardiovascular function in severe form of HMD, has not been studied in patients with mild HMD. Cerebral blood flow (CBF) may also be disturbed in patients with mild HMD; however, this has not been studied. There is a bulk of data that changes in CBF correlate well with an increased incidence of periventricular-intraventricular hemorrhage (PIVH) which may worsen the short-term and long-term prognosis of preterm infants with HMD.[4-6] With the availability of non-invasive technique to measure ventricular functions and CBF by echocardiography and Doppler technique,[7-9] it is possible to detect cardiovascular changes in patients with mild HMD and their response to dobutamine administration *in vivo,* which were also the purpose of this study.

METHODS

Design and study subjects

The study was conducted at Dr. Cipto Mangunkusumo Hospital, Jakarta, from November 1987 to May 1998. To be eligible for the study a preterm infant with mild HMD had to be more than 1250 grams in weight and less than 48 hours in age at the time of enrollment. Twins, patients with overt chromosomal syndrome, those with congenital heart disease other than patent ductus arteriosus, and those with congenital anomaly were excluded from the study.

The study comprised 2 parts. The first part was a cross sectional study to compare ventricular function (VF) and cerebral blood flow velocity (CBFV) of preterm infants with mild HMD and those without HMD. For this purpose, preterm infants with mild HMD were compared with their matched controls, i.e. preterm infants without HMD. The matching variables were birth weight (± 100 grams) and gestational age (± 2 weeks).

The second part was an interventional physiological study using randomized, double blind, placebo-controlled trial with cross-over design. For this purpose, all preterm infants with mild HMD who met the study criteria were subjects for VF and CBFV examinations. Thereafter, they were randomized by computer generated simple randomization scheme, to either receive a 30 minute administration of placebo or 10 µg/kg/minute dobutamine infusion (Dobutamine, Giulini®). Repeat VF and CBFV examination was done at the last minutes of the 30 minute infusion. Subsequently, other drug (i.e., dobutamine or placebo) was administered for 30 minutes, and VF and CBFV examination was repeated.

The diagnosis of HMD was based on clinical manifestations of respiratory distress syndrome (RDS) and chest X-ray examination. The clinical diagnostic criteria for RDS were (1) respiratory rate >60/minute; (2) intercostal retractions; (3) flaring of the alae nasi; (4) expiratory grunting; (5) cyanosis at room air.[10] Chest X-ray was done in every patient; a standard photo was obtained with the patient supine and the distance of 1 meter from x-ray source. The result was interpreted by the author and confirmed by a pediatric radiologist. The radiological criteria were (1) stage I: reticulo-granular pattern; (2) stage II: air bronchogram; (3) stage III: as stage II but more severe; (4) stage IV: white lung.[11]

For the purpose of this study patients with HMD were classified into 2 categories, i.e., patients with mild HMD (those who did not require mechanical ventilation), and patients with severe HMD (who required ventilation). The indication for mechanical ventilation support for HMD patients were: $PaCO_2$ >65 mmHg for babies >1500 grams or >50 mmHg for babies <1500 grams, with pH <7.2.[12] Sample size in each part of the study was estimated according to relevant sample size formula,[13] giving an estimate of subjects between 20 to 40 per group.

Measurements

Two-dimensional echocardiography

Two-dimensional echocardiography was performed in every patient to exclude the presence of congenital heart disease (CHD). Examination was performed with the patient supine without sedative, by using Aloka SSD 870, with 5 MHz and / or 3.75 MHz transducer. Segmental analysis was done; this included determination of atrial situs, veno-atrial, and atrio-ventricular connections. Cardiac chamber and great artery dimensions, as well as all leaflets were determined. The positions of the great arteries were sought for, as well as any defect in the atrial septum, ventricular septum, or the presence of patent ductus arteriosus (PDA). The latter was viewed form high left parasternal position, confirmed by color flow mapping for the presence of continuous flow at the duct or pulmonary artery. The

presence of coarctation of the aorta was excluded by suprasternal view examination.

Systolic function study

M-mode echocardiography was done for determining left ventricular (LV) function; this was done with the patient in supine position. In addition to electrocardiography (ECG), the monitor was supplied with apex-cardioghraphy with the transducer placed on the abdomen as a marker of the respiratory cycle. Examination was performed with the paper speed of 50-100 mm/sec. Three measurements were done in separate cardiac cycles during expiratory phase, and the results were averaged. The pre-ejection period (PEP) was measured from the q wave of the ECG and the beginning of the aortic valve opening, whereas left ventricular ejection time (LVET) was determined from the start of the opening to the aortic valve closure. PEP/LVET was then calculated. Since PEP and LVET are influenced by heart rate, both values were indexed for heart rate according to Levy,[14] using the formula: PEP(c) = PEP + 0.18 heart rate, and LVET(c) = LVET + 0.69 heart rate.

Diastolic function study

LV and RV diastolic function measurements were performed by Doppler technique; this was done simultaneously with two-dimensional and/or M-mode echocardiography to exclude abnormal flow pattern. A 5 and / or 3.5 MHz transducer was used, with the paper speed of 50-100 mm/sec. Diastolic filling was measured by placing the sample volume (gate 1.5 mm) at the tips of the mitral (for LV) or tricuspid (for RV) leaflets.[3] The parallelism of the ultrasonic beam and blood flow was obtained by positioning the transducer until a highest spectral flow was seen and clear sound was heard. E and A modal velocities (cm/sec) were recorded, and E/A ratio calculated. All measurements were done in expiratory phase in 3 separate cardiac cycles, and the results were averaged.

Cerebral blood flow velocity measurement

Cerebral blood flow velocity (CBFV) measurement was performed by pulsed wave Doppler and color flow mapping by using a 5 and/or 3.5 MHz transducer. With the baby in supine position, the transducer was placed at the anterior fontanel. After orientation, a sagittal view was obtained. Arterial pulsation was seen and the one with red color (indicating flow toward transducer) was selected. After obtaining the highest spectral flow, a maximal and minimal flows at the anterior cerebral artery were obtained. Pourcelot index was calculated by formula: Pourcelot Index = (Vmax - Vmin)/ Vmax.[7,8] All measurements were performed during expiratory phase in 3 separate cycles, and the results were averaged.

Patient management

All patients were put in an infant incubator with 35°C ambient temperature and 90% humidity. Intravenous 10% dextrose was given for water maintenance. Oxygen was administered through a nasal catheter or a head box with the flow of 2-4 liters/minute. Prophylactic antibiotic was given (IV amoxycillin 50 mg/kg/day). Monitoring of blood gas and electrolyte was done and correction was administered when indicated. Parental informed content was obtained from all patients. This study has been approved by the Ethical Committee on Medical Research, Medical School, University of Indonesia, Jakarta.

All data were compiled in a computer database using Epi-info 6 and SPSS (Statistical Package for Social Sciences) for Windows Release 6.0. VF and CBFV values in patients with mild HMD and in controls were compared by using paired t test. The same test was used to compare effects of dobutamine on VF and CBFV in patients with mild HMD. The level of significance was $p<0.05$, 2-tailed test.

RESULTS

Cardiovascular functions in patients with mild HMD

Comparisons of cardiovascular functions were obtained from 23 preterm infants with mild HMD and their matched controls without HMD. Table 1 disclosed that the RV diastolic function parameters were not significantly different between the 2 groups. The means of points E and A, and E/A ratio were 26 cm/sec, 33 cm/sec, and 0.83 respectively in healthy preterm infants, while those values were 24 cm/sec, 32 cm/sec, and 0.74 respectively in patients with mild HMD. It was noted that the RV E point was lower than A point in most subjects with and without mild HMD. On the other hand, the LV function parameters were significantly different between the 2 groups, although the E/A ratio was not (Table 2). In most patients, both patients with mild HMD and without HMD, point E of the LV was higher than point A, similar to that in older children and adults. Table 2 shows that the mean point E of the LV in preterm infants with mild HMD was 5

cm/sec lower than that in infants without HMD; this different was statistically significant. Similarly, the mean point A in preterm infants with mild HMD was 2.6 cm/sec lower than in control infants without HMD, and the difference was statistically significant. However the mean E/A ratio of the LV in infants with HMD and without mild HMD was not statistically significant (1.23 vs 1.16).

A significant difference between preterm infants with and without mild HMD was seen in systolic time intervals of the LV (indexed for heart rate), as seen in Table 3. Of 23 pairs of preterm infants, the mean rate-corrected PEP of the LV in preterm infants with mild HMD was 9 milliseconds longer than that in preterm infants without HMD, whereas the mean rate-corrected LVET in preterm infants with mild HMD was 10 milliseconds shorter than that in preterm infants without HMD. Both values were statistically significant. Similarly, the mean PEP/LVET ratio of both groups was significantly different.

Comparison of CBFV between preterm infants with and without mild HMD can be seen in Table 4. In only 20 out of 23 pairs of infants were the blood flow velocity records could be analyzed. There was no significant difference between the means maximal or minimal blood flow velocity as well as Pourcelot Index in both groups. Similarly, the mean blood flow acceleration in both groups was not statistically different.

Table 1. Comparison of right ventricular diastolic function between preterm infants with and without mild HMD (n=23)

RV diastolic function parameter	Without HMD Mean (SD)	With HMD Mean (SD)	p value*
Point E (cm/sec)	25.5 (9.60)	23.8 (9.30)	p = 0.419
Point A (cm/sec)	33.4 (11.32)	32.1 (9.82)	p = 0.634
E/A Ratio	0.83 (0.32)	0.74 (0.16)	p = 0.202

SD = standard deviation; *paired t test

Table 2. Comparison of left ventricular diastolic function in preterm infants with and without mild HMD (n=23)

LV diastolic functionparameter	Without HMD Mean (SD)	With HMD Mean (SD)	p Value*
Point E (cm / sec)	47.4 (9.47)	42.9 (8.11)	p = 0.003
Point A (cm / sec)	41.7 (11.41)	39.1 (10.22)	p = 0.022
E/A Ratio	1.23 (0.42)	1.16 (0.33)	p = 0.231

SD = standard deviation; *paired t test

Table 3. Comparison of systolic time intervals (STI) in preterm infants with and without mild HMD (n=23)

Left ventricular STI	Without HMD Mean (SD)	With HMD Mean (SD)	p value *
PEP(c) (millisec)	92.0 (9.18)	101.4 (7.10)	p = 0.000
LVET (c) (millisec)	256.0 (29.77)	245.9 (32.31)	p = 0.000
PEP / LVET	0.3240 (0.046)	0.3751 (0.040)	p = 0.000

PEP(c) = rate corrected pre-ejection period; LVET(c) = rate-corrected left ventricular ejection time; SD = standard deviation; *paired t-test

Table 4. Comparison of cerebral blood flow velocity (CBFV) in preterm infants with and without mild HMD (n = 20)

	Without HMD Mean (SD)	With HMD Mean (SD)	p value*
Maximum CBFV (cm/sec)	31.5 (7.31)	30.9 (7.20)	p = 0.738
Minimum CBFV (cm/sec)	8.4 (2.20)	8.6 (2.42)	p = 0.524
Pourcelot Index	0.7168 (0.12)	0.6909 (0.13)	p = 0.505
Acceleration (cm/sec^2)	98.3(10.82)	94.3 (8.81)	p = 0.132

SD = standard deviation; *paired t-test.

Effects of dobutamine on cardiovascular functions in patients with mild HMD

This part of the study aimed to determine the effects of dobutamine with a fixed dose of 10 µg/kg/minute in mild HMD patients by randomized double blind cross-over design. There were 41 preterm infants with mild HMD. Thirty-six were born in Dr. Cipto Mangunkusumo Hospital, while the other patients were referred by other health providers.

Vital signs

Following 30 minutes of infusion, the vital signs of dobutamine and control groups were significantly different. The mean heart rate of dobutamine group was 161 per minute vs 154 in controls. The mean respiratory rate decreased in dobutamine group (65 per minute), compared with 70 per minute in placebo group. The means of systolic, diastolic, and mean arterial pressures were significantly different between the 2 groups, i.e., 62, 29, and 40 mmHg respectively in placebo group vs. 68, 31, and 43 mmHg respectively in dobutamine group. See Table 5.

Table 5. Comparison of vital signs between dobutamine and placebo groups (n=41)

Vital sign	Placebo Mean (SD)	Dobutamine Mean (SD)	p value*
Heart rate (per minute)	154.2 (11.83)	160.5 (10.37)	p = 0.002
Respiratory rate (per minute)	69.5 (13.28)	64.9 (11.11)	p = 0.012
Systolic pressure (mmHg)	61.6 (4.86)	68.2 (4.52)	p = 0.000
Diastolic pressure (mmHg)	29.1 (2.98)	31.2 (3.28)	p = 0.001
Mean arterial pressure** (mmHg)	39.7 (2.88)	43.2 (2.93)	p = 0.000

SD = standard deviation; *paired t test; **mean arterial pressure = diastolic pressure + 1/3 (systolic - diastolic pressure)

Ventricular function

Parameters for RV diastolic function were collected in 34 patients. It appeared that the means points E and A, and E/A ratio were not significantly different between dobutamine and placebo groups. The administration of dobutamine only minimally increased the E and A points (Table 6). Those were not the case in LV, where dobutamine significantly increased the means points E and A, although the mean E/A ratio did not significantly change. See Table 7. Table 8 shows that LV systolic time intervals were also significantly different between dobutamine and placebo groups. Following the administration of dobutamine, the mean rate corrected PEP shortened from 104 to 96 milliseconds, the mean rate corrected LVET increased from 252 to 259 milliseconds, and the mean PEP/LVET ratio decreased from 0.37 to 0.32. Those changes indicated that LV function improved significantly with dobutamine administration.

Table 6. Comparison of right ventricular diastolic function between dobutamine and placebo groups (n=34)

RV diastolic function parameter	Placebo Mean (SD)	Dobutamine Mean (SD)	p value*
E point (cm/sec)	25.8 (8.72)	28.7 (8.72)	p = 0.106
A Point (cm/sec)	31.6 (9.29)	34.7 (8.99)	p = 0.120
E/A Ratio	0.7777 (0.175)	0.8281 (0.323)	p = 0.412

SD = standard deviation; *paired t-test

Table 7. Comparison of left ventricular diastolic function between dobutamine and placebo groups (n=34)

LV diastolic function parameter	Placebo Mean (SD)	Dobutamine Mean (SD)	p value*
E Point (cm/sec)	41.9 (8.52)	46.5 (10.45)	p = 0.003
A Point (cm/sec)	37.6 (9.45)	41.3 (10.16)	p = 0.000
E/A Ratio	1.17 (0.33)	1.19 (0.40)	p = 0.671

SD = standard deviation; *paired t-test

Table 8. Comparison of left ventricular systolic time intervals between dobutamine and placebo groups (n=34)

LV systolic time interval	Placebo Mean (SD)	Dobutamine Mean (SD)	p value *
PEP(c) milliseconds	103.9 (12.13)	96.2 (9.66)	p = 0.001
LVET(c) millisecond	251.6 (27.21)	259.3 (32.23)	p = 0.000
PEP/LVET	0.3718 (0.051)	0.3220 (0.041)	p = 0.000

PEP(c) = rate-corrected pre-ejection period; LVET(c) = rate-corrected left ventricular ejection time; SD = standard deviation; *paired t test

Cerebral blood flow velocity (CBFV)

Dobutamine did not change CBFV in 36 patients studied; the means maximal and minimal flow velocities and Pourcelot Index were not significantly different between dobutamine and placebo groups following dobutamine administration. On the other hand, dobutamine significantly increased the mean blood flow acceleration, from 93 to 96 cm/sec^2. See Table 9.

Table 9. Comparison of cerebral blood flow velocity (CBFV) between dobutamine and placebo groups (n=36)

	Placebo Mean (SD)	Dobutamine Mean (SD)	p value*
Maximun CBFV (cm/sec)	30.9 (8.34)	32.1 (7.58)	p = 0.101
Minimum CBFV (cm/sec)	7.7 (2.68)	8.1 (2.59)	p = 0.203
Pourcelot Index	0.7 (0.131)	0.75 (0.107)	p = 0.061
Acceleration (cm/sec^2)	92.9 (13.82)	95.8 (12.15)	p = 0.047

SD = standard deviation; *paired t-test

DISCUSSION

Changes of cardiovascular functions in HMD

The cardiovascular function is influenced by many factors, including pulmonary factors. In preterm infants, since the myocardium is immature, the cardiovascular response may be different from that in adult. Neonatal period is a transitional period from intrauterine to extrauterine life. This includes the circulation system. During the fetal period, the RV works as hard as, or even harder than the LV because it has to restrain the high pressure resulted from the undeveloped lungs. This condition will continue (but in a milder degree) after the baby is born because the pulmonary vascular resistance will start to decrease following lung inflation and some other physiological changes.[15] This condition can be observed more clearly in preterm infants. In HMD, diffuse atelectasis causes an increase of pulmonary vascular resistance.[16] As a result, to supply blood to the lungs, the right heart has to work harder. If the blood flow from the RV to the lungs is disturbed, the back flow to the left atrium will also be disturbed. That is why in severe HMD systolic and diastolic functions of both sides of the heart are disturbed.[17] On the contrary, cardiovascular abnormality in mild HMD has never been studied. This study is aimed mainly to identify cardiovascular abnormalities in mild HMD.

There were 4 measurements of cardiovascular functions used in this study, i.e. RV diastolic function (point E, point A, E/A ratio), LV diastolic function (point E, point A, E/A ratio), LV systolic function (PEP, LVET, PEP/LVET ratio)[18] and CBFV (maximum rate, minimum rate, Pourcelot index, and acceleration).[7-9] These parameters were chosen because they could be measured non- invasively and accurately with echocardiography and Doppler. LV function measurements with M-Mode echocardiography (i.e., LV internal dimensions, ejection fraction) which has very high validity and reliability in adults and older children, are proved to be inaccurate in newborn babies, due to unstable ventricular wall and septum characteristics.[19] For this reason, LV function examination with *M-mode* was not used in this study.

In RV diastolic function examination, the means point E, point A, and E/A ratio in patients with mild HMD were not different from those in preterm infants without HMD. The pattern of points E and A were also different from those in adults and older children. In older children, E wave, which represents early rapid filling phase from the right atrium to the RV, is higher than in point A (atrial phase). In preterm infants with or without HMD, point E was found lower than point A in most cases. Table 1 shows that in preterm infants without HMD the means of point E and A were not significantly different from those in preterm infants with HMD.

In Table 2 it is seen that the means of LV E and A points in preterm infants with HMD were lower than those in preterm infants without HMD, indicating a decreased LV filling in preterm infants with mild HMD. This condition is explainable since in HMD the pulmonary vascular resistance is increased which blocks the blood flow to the lungs with a consequence that the back flow to the left atrium decreases; as a result the LV filling in preterm infants with HMD is decreased.[19,20] A more clear situation is observed in infants with severe HMD, as mentioned earlier.[3] However, the mean E/A ratio in infants with HMD was not significantly different compared to that in preterm infants without HMD; this indicated that the decrease of early filling phase was parallel to the decrease of atrial filling phase. It is important to note that LV E and A wave patterns in preterm infants with HMD were similar to those in preterm infants without HMD, as normally seen in older children or adult (point E is higher than point A).

Systolic time intervals in patients with and without mild HMD (Table 3) show a significant difference. This shows that pulmonary function abnormalities in mild HMD give a negative effect to the LV systolic function, characterized by a prolonged PEP and shortened LVET. Since both PEP and LVET vary with heart rate, the two LV systolic function parameters were corrected for heart rate, as suggested by the experts.[14,18,19]

CBFV data in preterm infants with or without mild HMD show that the pattern and CBFV was not different, as were the Pourcelot Index and acceleration time (Table 4). This means that in mild HMD, immature autoregulation in preterm infants may still overcome the mild circulatory changes. As mentioned by Vergesslich et al.[21] autoregulation immaturity does not mean that the system is completely unresponsive to the circulatory and metabolic changes. Further discussion on CBFV and autoregulation system will be presented in the discussion of CBFV responses in patients with HMD *(vide infra).*

Effects of dobutamine on cardiovascular functions

Forty-one preterm infants with HMD were given placebo and dobutamine with *cross-over design*. This

design is beneficial since it reduces the number of subjects needed compared with parallel design.[22] With this cross design, 41 pairs of data were obtained, each pair was made from the same subjects which was given placebo and dobutamine (or the reverse) in consecutive order. This design needs certain conditions, (1) the disease or patient's condition is relatively stable, so that significant clinical or laboratory changes will not occur during intervention; (2) a wash out period is required to exclude the effect of the previously administered drug. In this study both requirements were fulfilled because: (1) placebo or dobutamine was only administered in 30 minutes, so that clinical or laboratory alterations were unlikely to occur significantly; (2) serum half life of dobutamine is very short, not more than 3 minutes.[23] Consequently specific wash out period was not required.

Dobutamine is a titrable inotropic agent with a rapid onset of action and a short period of action, so that its dosage could be adjusted according to therapeutic response. In this interventional study a fixed dose of 10 µg/kg/minute was used because of the following reasons. Firstly, the fixed dose omitted the need for dose titration, which was impractical since the study was performed in double blind manner. Secondly, although the therapeutic range of dobutamine is very wide, i.e., between 2 and 40 µg/kg/minute, most authorities believe that in general the effective dose of dobutamine is between 5-15 µg/kg/minute. Further, in one study to find out the optimal dose of dobutamine in preterm infants, it was found that the optimal dose was 10 µg/kg/minute.[23] The same dosage was also used by Stopfkuchen et al.[19] to study systolic time intervals in severe RDS.

Table 5 shows comparison of vital signs between both groups. Dobutamine administration changed mean heart rate and mean respiratory rate significantly, as well as the means systolic, diastolic, and mean arterial pressures. Increase in mean arterial pressure has been the expected effect of dobutamine administration, and has been used as a parameter for inotropic effect to increase blood pressure in preterm infants with hypotension.[23,24] It should be mentioned that in placebo group, the mean arterial pressure was 39 mmHg, while the critical value for mean arterial pressure in preterm infants is 30 mmHg.[24] It means that in this series no patient was hypotensive, which is commonly found in severe HMD. Increase in heart rate in study accords with the report of Barre et al.,[25] but inconsistent with other's,[24] that compared with dopamine, dobutamine increases mean arterial pressure without increasing heart rate significantly.

RV diastolic functions were compared in 34 pairs of infants with mild HMD. Table 6 shows that dobutamine administration increased mean point E minimally (from 26 to 29 mmHg), and also increased mean point A minimally (from 32 to 35 mmHg); both changes were not significant. Different results were found in the response of LV diastolic functions (Table 7). Data showed that dobutamine increased significantly the mean diastolic filling velocity, both point E (from 42 to 47 cm/sec) and point A (from 38 to 41 cm/sec).

Interpretation of ventricular diastolic function is not a simple one, since it is influenced by many factors, one of them is diastolic filling.[26] Theoretically inotropic drug with positive chronotropic effect may disturb ventricular diastolic function, because it decreases diastolic filling time. However, in study this not the case, because increase in points E and A was larger than increase of heart rate. In Table 5 and Table 7, the heart rate increased from 154.2 to 160.5 per minute (4%), whereas point E increased from 41.9 to 46.5 cm/sec (11%), and point A increased from 37.6 to 41.3 cm/sec (10%). Furthermore, LV diastolic function values approached those values in preterm infants without HMD (Table 2). This means that *pseudonormalization* of the LV diastolic function was unlikely to operate; instead, improvement of LV diastolic filling occurred in accordance with improvement of LV systolic function following dobutamine administration.

Systolic time intervals in dobutamine and placebo groups were investigated in 34 pairs of infants with mild HMD. It is seen in Table 8 that in dobutamine group, the means PEP, LVET, and PEP/LVET ratio differed significantly compared with values in placebo group. This was a direct effect of inotropic property of dobutamine.[19] Decrease in PEP, elongation of LVET, and decrease in PEP/LVET ratio indicated improvement in LV systolic function following dobutamine administration.

The results showed that dobutamine improved LV diastolic and systolic dysfunction in patients with mild HMD. The main property of dobutamine is positive inotropic effect by activation of β adrenergic receptors. β adrenergic receptors is a glycoprotein located in cell membrane and consists of 2 types, i.e., β-1 and β-2. In man, as in all mammals, β-1 receptors dominates all

receptors (80%). β receptor density in neonates is higher than in adults.[27]

Effects of dopamine and dobutamine on hypotension were studied in a double blind interventional study in preterm infants (gestational age <34 minggu) with hypotension (mean arterial pressure <30 mmHg).[28] All patients had HMD and received surfactant. With the initial dose of 5 μg/kg/minute, the dose was increased 5 μg/kg/minute every 20 minutes. It was seen that dopamine increased mean arterial pressure better than dobutamine. In a dose of 10 μg/kg/minute, dopamine increased the mean arterial pressure to normal level in 30 of 31 subjects, whereas in the same dose dobutamine could only overcome hypotension in 22 of 32 subjects. Subjects who had failed to dobutamine administration showed positive response upon dopamine administration.

Roze et al.[23] compared dopamine and dobutamine in 20 preterm infants with gestational age of <32 weeks with the initial dose of 5 μg/kg/minute and maximal dose of 20 μg/kg/minute. Dopamine increased mean arterial pressure from 24 to 32 mmHg in a dose of 12.5 μg/kg/minute, whereas dobutamine failed to increased blood pressure in 6 patients, who then responded with dopamine administration. It is concluded that dopamine is better than dobutamine to treat hypotension in preterm infants.

Our data showed the difference of the response of RV diastolic filling following dobutamine administration. This might be explained by the fact that physiologically in preterm infants without HMD the RV diastolic filling (point E) is shorter than point A. In adult this pattern is called as a restrictive pattern, that may occur in myocardial dysfunction such as myocardiopathy or in increased pulmonary vascular resistance. Indeed, pulmonary vascular resistance is high in patients with HMD, so that the RV diastolic functions pattern resembles the restrictive pattern. Dobutamine administration activates β-1 receptors to increase myocardial contractility; however, since pulmonary vascular resistance did not decrease significantly, the restrictive pattern did not change. This is a more rational explanation than that the RV myocardium is thinner than the left one, since in newborn babies, especially in preterm infants, the right and left ventricles have similar thickness and load.[29] Other possibility is that the effect of dobutamine on pulmonary vascular resistance is less than its effect on peripheral vascular resistance.[30]

Dobutamine and cerebral blood flow in HMD patients

Improvement of LV function in patients with mild HMD following dobutamine administration was not followed by the same change of CBFV. Table 9 shows that maximum and minimum CBF as well as Pourcelot index did not differ significantly in patients with and without mild HMD. The only CBF parameter which showed significant difference was CBF acceleration, i.e., 93 cm/sec^2 in placebo group and 96 cm/sec^2 in dobutamine group.

Discussion on changes of CBFV and dobutamine effects on it in preterm infants should start with a specific characteristic of cerebral circulation, i.e., autoregulation mechanism. This mechanism is responsible for maintaining a relatively constant blood flow in the occurrence of perfusion and metabolic changes by vasoconstriction in the presence of increased perfusion pressure and vasodilation in decreased perfusion.[8,31] Autoregulation will allow vasodilation in acidosis, because acidosis decreases CBF.

In the last decade CBF has drawn many researchers. In the field of pediatrics, studies on CBF has been performed mainly in preterm infants, since infants in this group are prone to develop periventricular-intraventricular hemorrhage (PIVH), and is associated with immature CBF autoregulation. A simple examination of CBF which is non-invasive, non-radiation, relatively cheap, and can be performed at bedside is Doppler technique. This technique gives an accurate result as long as several requirements are met.[9,32] With this technique, we measure cerebral blood flow velocity (CBFV) instead of cerebral blood flow (CBF); however CBFV in most situations represents CBF.

Numerous studies show that autoregulation system in preterm infants has not functioned normally.[33] In general CBF increases with an increase of maturation in accordance with metabolic rate and energy requirements. Several conditions may alter CBF in preterm infants. Mechanical ventilation, both conventional and high frequency oscilation could change CBF pattern. Vergesslich et al.[21] studied 15 infants with mechanical ventilation to detect risk factors for cerebral hemorrhage. Subjects were infants with or without mechanical ventilation and have relatively stable mean arterial pressure. Data show that CBF in patients with mechanical ventilation does not change significantly as long as acid base can be maintained in relatively constant levels.

Changes in CBF are more clearly seen in preterm infants treated with extracorporeal membrane oxygenation (ECMO).[34] Other therapeutical procedures associated with changes of CBF that increase the risk for the development of PPIV is the use of surfactant in HMD, and indomethacin administration commonly used for closing PDA in preterm infants. Despite its physiological advantage of surfactant that improves ventilation-perfusion, rapid surfactant administration may lead to alter CBF significantly. It is concluded that surfactant administration causes sudden decrease of pulmonary vascular resistance and right to left shunt through PDA. This sudden change in mean arterial pressure and CBF may responsible for the development of PPIV in preterm infants treated with surfactant. Similar results were reported by others,[35,36] i.e., increase in CBF and PCO_2 following surfactant administration, so that strict acid-base monitoring is a must during administration of surfactant.

Effect of indomethacin administration on CBF has been reported.[37] Some routine procedures also may alter CBF. Lundstrom et al.[38] studied 70 preterm infants with the gestational age of less than 33 weeks in a randomized study. Subjects in Group I were treated in room air with the administration of oxygen whenever needed, while the other group was given 80% oxygen. It was found that routine oxygen administration in such infants did more harm than benefit to the infants.

There has been no report of the effects of dobutamine on CBF in preterm infants with mild HMD. Our data show that dobutamine administration did not alter CBFV in spite of significant changes in LV function, indicating that immature autoregulation mechanism in preterm infants with HMD could cope with the increase of cardiac output following dobutamine administration. Most patients in this study were in a stable acid-base condition, so that similar to in the use of mechanical ventilation, a stable acid-base can maintain autoregulation system to prevent untoward changes.[21] Increased CBF acceleration following dobutamine administration indicates that dobutamine has positive inotropic effect in mild HMD.

CONCLUSIONS

Data from this study indicate that: (1) In mild HMD there is no RV diastolic dysfunction, and dobutamine does not change the diastolic function; (4) In mild HMD there is a LV diastolic and systolic dysfunction, and administration of dobutamine improves those ventricular dysfunctions; (5) In mild HMD the CBFV is not altered, and dobutamine does not change the CBFV but does increase significantly the acceleration time of the flow.

Results of this study and previous knowledge warrant the following recommendations: (1) Dobutamine 10 µg/kg/minute may be given early in the course of mild HMD patients; (2) Further studies are needed to confirm findings in this study, as well as to determine the role of other inotropics and other cardiovascular drugs on the clinical course of this important disease.

Acknowledgments

The author wishes to thank Professor Hans E Monintja, MD, Professor Sofyan Ismael, MD, and Professor Bambang Madiyono, MD for continuously supervising the study and reviewing the article, to Asril Aminullah, MD and the Perinatology Staff for supervising patient management, to Kemas Firman, MD, for performing ultrasonographic examination, and to Dyani Kusumowardhani, MD for helping with manuscript preparation. This study was partly funded by "Tim Manajemen Program Doktor" (Department of Education and Culture, Republic of Indonesia), South-East Regional Office (SEARO) - WHO, Manila, The Management of "Riset Bimbingan Ilmu Pengetahuan dan Teknologi Kedokteran" (National Research Council), PT Solvay Pharmaceutical Indonesia, PT Dexa-Medica, and PT Kimia Farma. Dobutamine and placebo were prepared and supplied by Solvay Pharmaceutical, Hannover, Germany.

REFERENCES

1. Hjalmarson O. Epidemiology and classification of acute neonatal respiratory disorders. Acta Paediatr Scand 1981; 70:773-8.
2. Milenin OB, Efimov MS. Disorders of hemodynamics in the acute period of respiratory distress syndrome (Doppler echocardiography). Pediatriia 1990; 6:45-50. [Abstr].
3. Riggs TW, Rodriguez R, Snider AR, Batton D. Doppler echocardiographic evaluation of right and left ventricular diastolic function in normal neonates. J Am Coll Cardiol 1989; 13:700-5.
4. Volpe JJ. Intraventricular hemorrhage and brain injury in the premature infant. Neuropathology and pathogenesis. Clin Perinatol 1989; 16:361-86.
5. Volpe JJ. Intraventricular hemorrhage in the premature infants - current concepts. Ann Neurol 1989; 25:3-11 dan 109-16.
6. Jongmans M, Mercuri E, de Vries L, Dubowitz L, Henderson SE. Minor neurological signs and perceptual motor difficul-

ties in prematurely born children. Arch Dis Child Fetal Neonatal 1997; 76:F9-14.
7. Ohlsson A, Fong K, Ryan ML, Yap L, Smith JD, Shennan AT, *et al.* Cerebral blood flow velocity measurements in neonates: technique and interobserver reliability. Pediatr Radiol 1991; 121:395-7.
8. Blakenberg FG, Loh N-N, Nurbash AM, Craychee JA, Spielman DM, Person BL, *et al.* Impaired cerebrovascular autoregulation after hypoxic-ischemic injury in extremely low-birth-weight neonates: detection with power and pulsed wave Doppler US. Radiology 1997; 205:565-8.
9. Winkler P, Helmke R. Major pitfalls in Doppler investigations with particular reference to the cerebral vascular system. Part I. Sources of error, resulting pitfalls and measures to prevent errors. Pediatr Radiol 1990; 20:219-28.
10. Roberton NRC. A manual of neonatal intebsive care. London: Edward Arnold; 1993.
11. Weisenberg RL. The newborn chest. New York: Harper & Row; 1973. p. 55-70.
12. Brady JP, Gregory GA. Assisted ventilation. In: Klauss MH, Fanaroff AA, editors. Care of high-risk neonate. 3rd edition. Philadelphia: Saunders; 1986. p. 202-18.
13. Meinert CL. Clinical trials - design, conduct, and analysis. New York: Oxford University Press; 1986. p. 81-4.
14. Levy AM, Leaman DM, Hanson JS. Effects of digoxin on systolic time intervals of neonates and infants. Circulation 1972; 46:816-23.
15. Clark EB. Growth, morphogenesis, and function: the dynamic of cardiac development. In: Moller JH, Neal WA, editors. Fetal, neonatal, and infant cardiac disease. Connecticut: Appleton & Lange; 1990. p. 73-92.
16. Skinner JR, Boys RJ, Hunter S, Hey EN. Pulmonary and systemic arterial pressure in hyaline membrane disease. Arch Dis Child 1992; 67:366-73.
17. Martin RJ, Fanaroff AA. The respiratory distress syndrome and its management. In: Fanaroff AA, Martin RJ, editors. Neonatal-perinatal medicine. Diseases of the fetus and infant. 6th edition. St Louis: Mosby; 1997. p. 1018-27.
18. Braunwald E. Assessment of cardiac function. In: Braunwald E, editor. Heart disease - a textbook of cardiovascular medicine. 3rd edition. Philadelphia: Saunders; 1988. p. 419-43.
19. Stopfkuchen H, Queisser-Luft A, Vogel K. Cardiovascular responses to dobutamine determined by systolic time intervals in preterm infants. Crit Care Med 1990; 18:722-4.
20. Banner Jee A, Brook MM, Klautz RJ, Teitel DF. Nonlinearity of left ventricular and systolic wall stress velocity of fiber shortening in young pigs: a potential pitfall in its use as a single-beat index of contractility. J Am Coll Cardiol 1994; 23:514-24.
21. Vergesslich KA, Weninger M, Ponhold W, Simbruner G. Cerebral blood flow in newborn infants with and without mechanical ventilation. Pediatr Radiol 1989; 19:509-12.
22. Pocock SJ. Clinical trials - a practical approach. New York: John Wiley & Sons; 1991. p. 123-38.
23. Roze JC, Tohler C, Maingueneau C, Lefevre H, Mouzard A. Response to dobutamine and dopamine in hypotensive very preterm infant. Arch Dis Child 1993; 69:59-63.
24. Martinez AM, Padbury JF. Dobutamine pharmacokinetics and cardiovascular responses in critically ill neonates. Pediatrics 1992; 89:47-51.
25. Barre J, De Baker D, Moraine JJ, Melot C, Kahn RJ, Vincent J-L. Dobutamine increases cerebral blood flow and jugular bulb hemoglobin saturation in septic patients. Crit Care Med 1997; 25:392-8.
26. Nishimura RA, Hayes DL, Holmes DR Jr, Tajik AJ. Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: an acute Doppler and catheterization hemodynamic study. J Am Coll Cardiol 1995; 25: 281-8.
27. Birk E. Myocardial receptors. In: Gluckman PD, Heymann MA, editors. Pediatric and perinatology - the scientific basis. 2nd edition. London: Arnold; 1996. p. 725-8.
28. Klar JH, Faix RG, Pryce CJ, Bhatt-Mehta V. Randomized, blind trial of dopamine versus dobutamine for treatment of hypotension in preterm infants with respiratory distress syndrome. J Pediatr 1994; 125:117-22
29. Heymann MA. Fetal and postnatal circulations: Pulmonary circulation. In: Emmanouilides GC, Riemenschneider TA, Allen HD, Gutgessel HP, editors. Moss and Adams Heart disease in infants, children, and adolescents. 4th edition. Baltimore: Williams & Wilkins; 1995. p. 41-7.
30. Freed MD. Congestive heart failure. In: Fyler DC, editor. Nadas' Pediatric cardiology. Singapore: Info-Access; 1992. p. 63-72.
31. Nelle M, Hoecker C, Linderkamp O. Effects of bolus tube feeding on cerebral blood flow velocity in neonates. Arch Dis Child Fetal Neonatal 1997; 76: F54-6.
32. Winkler P, Helmke K, Mahl M. Major pitfalls in Doppler investigations. Part II. Low flow velocities and colour Doppler applications. Pediatr Radiol 1990; 20:304-10.
33. Menke J, Michel E, Hillebrand S, von Twickel J. Cross-spectral analysis of cerebral autoregulation dynamics in high risk preterm infants during the perinatal period. Pediatr Res 1997; 42:690-9.
34. Walker LK, Shoirt BL, Traystman RJ. Impairment of cerebral autoregulation during venovenous extracorporeal membrane oxygenation in the newborn lamb. Crit Care Med 1996; 24:2001-6
35. Saliba E, Nashashibi M, Vaillant M-C, Nasr C, Leugler J. Instillation rate effects of Exosurf on cerebral and cardiovascular haemodynamics in preterm neonates. Arch Dis Child 1994; 71: F174-8.
36. Skinner J. The effects of surfactant on hemodynamics in hyaline membrane disease. Arch Dis Child 1997; 76:F67-9.
37. Austin NC, Pairaudeau PW, Hames TK, Hall MA. Regional cerebral blood flow velocity changes after indomethacin infusion in preterm infants. Arch Dis Child 1992; 47:851-4.
38. Lundstrom KE, Pryds O, Greisen G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Arch Dis Child Fetal Neonatal 1995; 73:F81-6.