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Myocardial Lactate Metabolism in Children with Non-Cyanotic Congenital Heart Disease

Toshiyuki Itoi

*Department of Pediatric Cardiology and Nephrology,
Graduate School of Medical Science,
Kyoto Prefectural University of Medicine
Japan*

1. Introduction

It is well recognized that main energy source for myocardium is fatty acids (Wisneski et al., 1987, Lopaschuk et al., 2010). However, in failing heart or in hypertrophied heart, fatty acid oxidation ability was reported to be impaired and, on the contrary, carbohydrates were preferred to use for provision of energy demand (Stanle et al., 2005, Lopaschuk et al., 1992). The fetal heart is exposed to relatively high lactate concentrations. Immediately after birth, plasma lactate concentrations decrease. In the immature heart, *lactate dehydrogenase (LDH)* is predominated by the M type isozyme, as higher activity, resulting in greater lactate production from pyruvate (Brooks et al., 1985). This requires greater NADH levels than seen in the adult heart. The dominance of glycolytic flux in immature hearts leads to accumulation of lactate to a greater extent than is seen in adult hearts during profoundly hypoxic states (Brooks et al., 1985).

It has been shown that, in the isolated perfused rat heart, lactate significantly contributes to acetyl-CoA formation more than glucose. When fatty acid oxidation is activated, pyruvate dehydrogenase (PDH) activity is suppressed by increase of the NADH/NAD⁺ ratio followed by an enhancement of lactate production from accumulated pyruvate. As a result, lactate is released from myocardium even under aerobic status (Brooks et al., 1985). Immediately after birth, fatty acids are not the major energy substrate in newborn hearts, although the capacity of the heart for oxidization of fatty acids rapidly increases. Of interest, lactate is also important ATP provider in newborn heart (Lopaschuk et al. 1991).

Patho-physiology of congenital heart defects (CHD) is very wide ranging from the right ventricular (RV) volume overload and/or pressure overload to the left ventricular (LV) volume overload and/or pressure overload. CHD with left-to-right shunt is basically a non-cyanotic status. However, the myocardial cells may be in the milieu of relatively low oxygen because of relative decreased of coronary circulation from hypertrophy. Despite the evidence that lactate may be an important fuel for myocardial energy metabolism, there is remarkably little information on the lactate utilization in immature hearts especially in CHD. Lactate plays the other important role as a regulator of cellular redox state. *The redox state described in this chapter is defined as the balance of NADH/NAD⁺ in the myocardium.* The cytosolic NADH/NAD⁺ ratio in most tissues is enhanced by activation of glycolysis. If lactate dehydrogenase (LDH) activity is high such as in heart, the lactate/pyruvate (L/P)

ratio of a given cell is regarded to reflect the cytosolic NADH/NAD⁺ ratio. The lactate and pyruvate are thought to provide for a redox coupling between organs through blood since plasma level of these metabolites equilibrate with cytosolic concentrations of cells. In view of "lactate shuttle theory" by Brooks (Brooks, 2002), lactate released into the coronary venous circulation and taken up by distal tissue that is to say myocardium via coronary artery circulation may affect redox state in the myocardial cells.

The energy substrates use in CHD had been focused on cyanotic disease (Scheuer et al., 1970, 1972, Rudolph et al., 1971, Fridli et al., 1977). As such, the studies of myocardial metabolism have long history but are very limited (Scheuer et al., 1970, 1972, Fridli et al., 1977, Åmark et al., 2007). In recent years, advancement of intensive care before and after surgical treatment, and carrying out of the long-term care of the circulation are getting to require precise *understanding* of myocardial metabolism in CHD.

In this article, we focused on myocardial use of energy substrates, especially lactate, in young patients with RV volume overload (*represented in the atrial septal defect, ASD*) or with both RV pressure load and LV volume load (*represented in the ventricular septal defect, VSD*). The author will also consider the myocardial redox state of non-cyanotic CHD in young patients with reviewing of myocardial substrate use.

2. Patients and methods

Twenty one patients were enrolled into this study. Their ages range from ten-month to 11 years: patient details are summarized in Table 1. The patients were divided into three groups; Seven patients of Kawasaki disease without coronary lesions over 6 months after healing (KD group), seven patients of ASD as a representative of RV volume overload (ASD group), (*ASD group*), seven patients of VSD or patent ductus arteriosus (PDA) as a representative of RV pressure overload in addition to LV volume overload (PH group). (*PH group*). *All the patients in the PH group were received diuretics.*

All patients were not fed for at least four hours. Combination of ketamine-HCl and diazepam were used for general anesthesia with spontaneous respiration. Heparin (100U/kg) was administered after insertion of arterial sheath. Intravenous infusion including 4.3% glucose and 20 mEq/l lactate maintained during the protocol. A coronary sinus catheter was inserted into the mid-to-anterior region of the coronary sinus via the inferior vena cava under fluoroscopy (Hamaoka et al., 1989). Blood sample collection was done at least 10 min after the end of all catheterization and angiography for the diagnosis because the influence of contrast medium to myocardial metabolism was reported to maintain 10-20 minutes by Wisneski et al (Wisneski et al., 1982). The verification of appropriate catheter position was determined by measuring oxygen saturation.

Oxygen saturation was measured by Oxygen Saturation Monitor system (Erma). Blood samples were obtained simultaneously from coronary sinus and femoral artery for the chemical analysis of concentrations of glucose, lactate and free fatty acids and oxygen concentration. Blood samples for glucose were mixed with titrate and, for lactate and pyruvate with 6% perchloric acid. This protocol was performed by the guideline of the Committee on Research of Kyoto Prefectural University of Medicine and informed consents were obtained from parents.

Calculations on energy substrate metabolism:

Pulmonary blood flow to systemic blood flow ratio (Q_p/Q_s) was calculated by means of Fick's method. Blood oxygen concentration was calculated as the product of Hb

concentration, oxygen saturation, and an oxygen-binding capacity of 1.34 ml/g. The oxygen extraction rate (OER) for each substrate was calculated using the following formula:

- $OER = (AVD_{\text{substrate}} / AVD_{\text{oxygen}}) \times \text{substrate factor}$
- AVD; arteriovenous concentration difference

The substrate factor for glucose or lactate is 0.75 and 5.7 for free fatty acids (FFA). FFA concentration of whole blood was calculated by multiplying plasma concentration with (100-hematocrit)/100.

Redox potential (Eh) = $-204 + 30.7 \times \log([pyruvate]/[lactate])$ (Gudbjarnason & Bing, 1962).

$\Delta Eh = Eh_{cv} - Eh_{ao}$ (Eh_{cv} and Eh_{ao} represent Eh of coronary venous blood and of aortic blood, respectively)

Statistical analysis

Values are expressed as mean \pm standard deviation. All statistical tests were performed using JMP (ver.6, SAS Institute Japan, Co). We used Kruskal-Wallis one way analysis of variance on ranks to compare overall differences among three groups. We compared median value of all groups using two tailed Mann-Whitney U tests. Because three pairwise planned comparisons were made we considered $P < 0.016$ as significant. In case of comparison of paired samples, Wilcoxon signed-rank test was applied and $P < 0.05$ was considered as significant.

3. Results

3.1 Patients profiles (Table 1)

There was no significant difference among the groups on age. Heart rates (HR) and left ventricular systolic pressure (LVSP) were similar among groups, so the double products (LVSP \times HR) of the left ventricle in PH group was same to those in ASD group. The ratio of the right ventricular systolic pressure (RVSP) to the LVSP was higher in PH group than in ASD group (0.35 ± 0.13 mmHg vs 0.79 ± 0.17 mmHg). Q_p/Q_s of 1.7 ± 0.5 in PH group was also the same level in comparison with that of 1.8 ± 0.2 in ASD group.

3.2 Oxygen uptake

The arterial-coronary vein oxygen concentration differences were similar among three groups; 11.1 ± 0.7 Vol% for KD, 11.1 ± 2.3 Vol% for ASD group, and 10.9 ± 0.9 for PH group. However, this does not mean that the myocardial oxygen consumption of each group was similar, because we could not measure coronary flow in each group. Among three groups, however, the similar LV double products value may suggest the same levels of the LV oxygen consumption. On the other hand, the RV double products of the PH group were the highest level. These results suggested that the myocardial oxygen consumption in PH group may be the highest level among the groups.

3.3 Myocardial substrate uptake

The concentrations of glucose, lactate, and FFA in the artery were same levels among the groups (Table 2). Plasma FFA concentrations were thought to be higher levels in all groups than normal values due to heparinization, although blood FFA was not measured before heparin injection. Concerning substrate concentrations in the coronary vein, lactate levels of PH group was significantly higher than other groups. Pyruvate concentrations of PH group showed no significant difference in comparison with values of other groups. Continuous

infusion of low dose lactate and glucose did not influence the concentrations of both lactate and glucose since blood levels of those substrates were within the normal values.

We calculated myocardial OER of each substrate since, in this study, coronary sinus blood flow could not be measured. Figure 1 shows OER of each substrate in each group. Glucose OER in each patient was quite variable so that there was no significant difference on the mean value; $2.0 \pm 13.0\%$ for KD group, $8.4 \pm 11.0\%$ for ASD group, and $15.5 \pm 20.4\%$ for PH group. Mean arterio-venous difference of lactate in PH group was negative resulting in $-5.3 \pm 11.2\%$ of calculated lactate OER. This value was significantly lower than both of KD group ($7.8 \pm 9.2\%$, $p=0.013$) and of ASD group (19.7 ± 9.5 , $p=0.004$). On the other hand, the lactate OER of ASD group showed higher trend than both KD group and PH group. There were no significant difference on FFA OER in each group; $62.8 \pm 28.2\%$ for KD group, $63.6 \pm 9.8\%$ for ASD group, and $62.8 \pm 28.0\%$ for PH group. Sum of each glucose, lactate, and FFA OER was calculated as a total OER of heart.

3.4 Myocardial redox state or anaerobic metabolism (Table 3)

The lactate/pyruvate (L/P) ratios in coronary vein were similar among the groups. However, the L/P ratios of both ASD group and PH group were relatively higher values than those of KD group. Each values of redox potential (Eh) calculated from blood lactate and pyruvate showed no significant difference among groups. The ΔEh also showed no significant difference among the groups but the ΔEh of PH group was relatively lower value than other groups.

3.5 The effects of oxygen inhalation

As some patients in PH group were supposed myocardial relative ischemia or hypoxic state, we measured the major energy substrates under administration of oxygen for CHD patients. Figure 2 demonstrates the change of lactate OER both from ASD group and PH group. Lactate OER of ASD group did not change with oxygen inhalation. On the other hand, its PH group increased from $-6.3 \pm 10.9\%$ to $3.0 \pm 9.9\%$. However, of interest, both the CS L/P ratio and ΔEh of each group showed no remarkable changes even after inhale of oxygen (Table 3).

4. Discussion

4.1 Characteristics of methodology on myocardial energy metabolism study

In humans, the coronary sinus, which empties into the right atrium, receives blood from 96% of veins from the left ventricular free wall and septum (Sethna et al., 1986). The coronary sinus system drains approximately three fourths of the blood entering the left coronary artery and only 10 to 20 % of the inflow of the right coronary artery. The rate of tissue metabolism (uptake or release) can only be measured by multiplying the artery-coronary vein difference by the blood flow if the flow, the arterial concentration, and the rate of tissue metabolism are all constant. We did not measure coronary sinus blood flow in this study because of technical difficulties for infants. Then, we calculated oxygen extraction ratio for standardizing and comparing the substrate use in the heart.

This kind of studies to adult patients carried without heparinization but with frequent wash of catheter for prevention of thrombus formation, since it is well known that heparin induces the production of free fatty acids from lipoprotein by activation of lipoprotein lipase. We used, in this study, heparin for anti-coagulation and obtained blood samples

under heparinized state because of two reasons; 1) for preservation of veins and arteries from obstruction in younger children and 2) for our aim of studying myocardial metabolism in patients under critical states as in pediatric intensive care unit or in surgical intervention where many patients were heparinized.

In spite of these limitation, this method we applied here is still useful for clinical study on myocardial metabolism (Vánky et al. 2006) because data obtained are supposed not far from animal model study (Lopaschuk et al., 1992), computer simulation study and isotopical study in human.

4.2 Myocardial use of lactate and other substrates in non-cyanotic CHD

It is very important to know the myocardial energy substrate use *during the management of heart failure* or cardiac surgery of children with CHD. However, myocardial metabolism even in the normal immature heart has not been fully elucidated. Although data we can refer on myocardial energy substrate use in normal children are limited, myocardial fatty acids uptake of KD group *resembles the results that Rudolph demonstrated* (Rudolph et al., 1971). For this reason, we considered that results from KD group represented normal myocardial substrate use in children. Table 4 shows the comparison among some previous reports on the substrates use in hearts in young including cyanotic CHD. Myocardial FFA uptake in children shows very similar levels among the reports. The very variable glucose uptake shown in other reports including adults suggested that glucose may not play an important role for myocardial energy supply for children at rest. (Vánky et al. 2006, Lopaschuk et al., 1992).

It has been demonstrated that adult hypertrophied hearts prefer to oxidize glucose. Increase of glucose oxidation may be beneficial for hypertrophied heart on production of ATP with less myocardial oxygen consumption than fatty acid oxidation. Allard *et al* reported that the steady-state palmitate oxidation rates were decreased in the hypertrophied hearts compared with control hearts (Allard et al., 1994). Although the uptake of glucose of CHD hearts, in our study, was quite variable, both hearts with the volume overloaded RV (ASD group) and with the pressure overloaded RV (PH group) showed tendency of increase of glucose uptake. (Figure 1, Table 4). These suggest that a myocardial potential of glucose use in children with CHD may not be an inferior level in comparison with adult hearts against overload. However, *one should note in our results that* FFA use was high levels even in PH group and that lactate was dominant energy supplier more than glucose in ASD group.

Gertz *et al* have reported that in subjects with high blood free fatty acids, myocardial lactate extraction may be low (Gertz et al., 1980). However, this is not the case at least in children with CHD (Table 4). The lactate use including of cyanotic CHD is relatively high even under the high levels of fatty acid use. From another point of view, it is speculated that fatty acid use in children with CHD *have reached to near maximum levels* and, as a result, lactate regulated the energy supply against additional loads on the heart. Some studies have clarified that fatty acids oxidation increased with elevation of ventricular workload in immature hearts (Itoi et al., 1993a, Ascuitto et al., 1999). The lactate oxidation rates of the immature hearts were also increased by the addition of preload to the RV without significant change of glucose oxidation (Itoi et al., 1993b). The ASD group in our study showed the very same result of this experimental model on change of the lactate oxidation (Figure 1). Recently, Vánky *et al* revealed that no significant uptake of glucose was detected before or after surgery for aortic stenosis but the uptake of lactate was significant before surgery (Vánky et al. 2006).

The blood lactate levels in the resting state are low, in the range of 0.5-1 mM, in human adults. Results of our study showed that, even in children with CHD, arterial lactate levels were the same as in adults (Table 2). Then, the lactate use changes in hearts of children with non-cyanotic CHD might not be influenced by blood lactate levels. Lactate oxidation occurs because the lactate dehydrogenase (LDH) isozyme found in heart has a low affinity for pyruvate, although the equilibrium constant for the LDH is in the direction of lactate formation. In addition, the hydrogen ion, pyruvate, and NADH formed by the LDH reaction are rapidly removed in the aerobic heart, forcing the reaction in the direction of the formation of pyruvate (Drake-Holland, 1983). Furthermore, in the setting of a fully activated FFA oxidation, glycolysis flux and the pyruvate dehydrogenase complex (PDC) activity are suppressed with increased NADH from β -oxidation. This phenomenon may result in not only deceleration of glucose oxidation but also acceleration of lactate oxidation (Figure 3). This scenario may happen in mildly overloaded hearts as in ASD group.

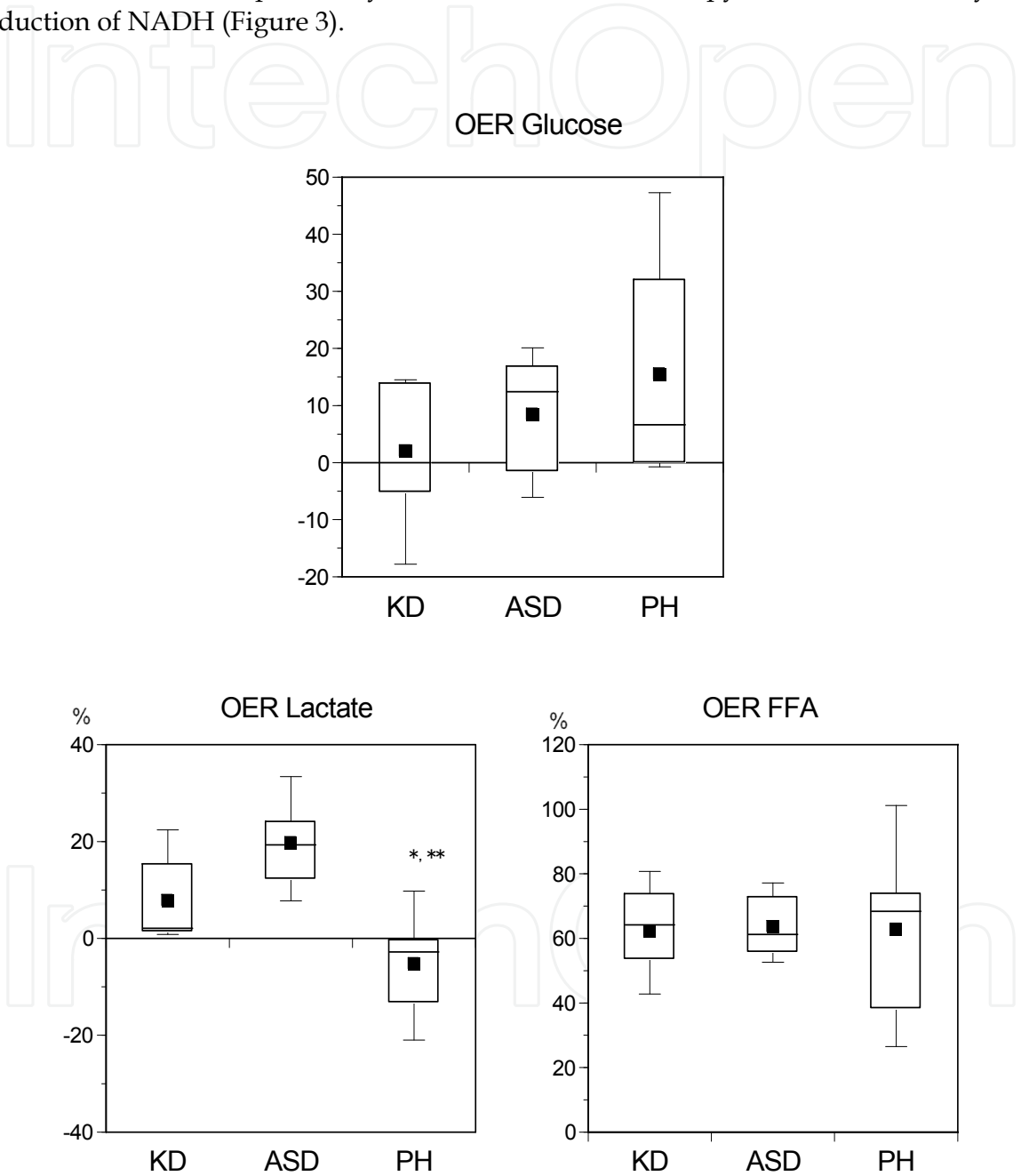
The very characteristic finding in our study was the efflux of lactate under the stable fatty acids use in PH group (Figure 1). In RVH, there is a mitochondrial metabolic switch from glucose oxidation to glycolysis due to myocardial ischemia (Pio et al., 2010, Gomez et al., 2001). Positron emission tomography studies in patients with RVH suggested that there is increased RV glucose uptake, which is thought to reflect enhanced glycolysis. The less efficient production of ATP by glycolysis in RVH meant the formation of lactate, rather than pyruvate (Oikawa et al., 2005). In the immature heart, lactate dehydrogenase (LDH), which is predominated by the M type isozyme, as higher activity, resulting in greater lactate production from pyruvate (Brooks et al., 2002). This requires greater NADH levels than seen in the adult heart. The dominance of glycolytic flux in immature hearts leads to accumulation of lactate to a greater extent than is seen in adult hearts during profoundly hypoxic states (Brooks et al., 2002). Now, does the spillover of lactate from hearts of PH group indicate the existence of profound myocardial ischemia of the right ventricle?

4.3 Redox-potential of the lactate-pyruvate system in CHD

The redox-potential of the coronary sinus blood approaches that of cardiac tissues, and the redox-potential of the coronary venous blood becomes more negative than that of arterial blood. When ΔE_h is positive there is active cellular oxidation and the energy required is supplied by oxidative phosphorylation. When ΔE_h is negative there is glycolysis and anaerobic phosphorylation becomes an important energy source (Gudbjarnason & Bing, 1962). The RV overloaded heart, especially PH group, showed a tendency of decrease of ΔE_h (Table 3). Since some hearts of CHD were supposed to be under hypoxic state, we administered oxygen to patients. The results that oxygen inhalation increased influx of lactate (Figure 2) without changes of both the L/P ratio and ΔE_h (Table 3) suggested that myocardial hypoxic state may not be only one cause of the lactate efflux from hearts of the PH group.

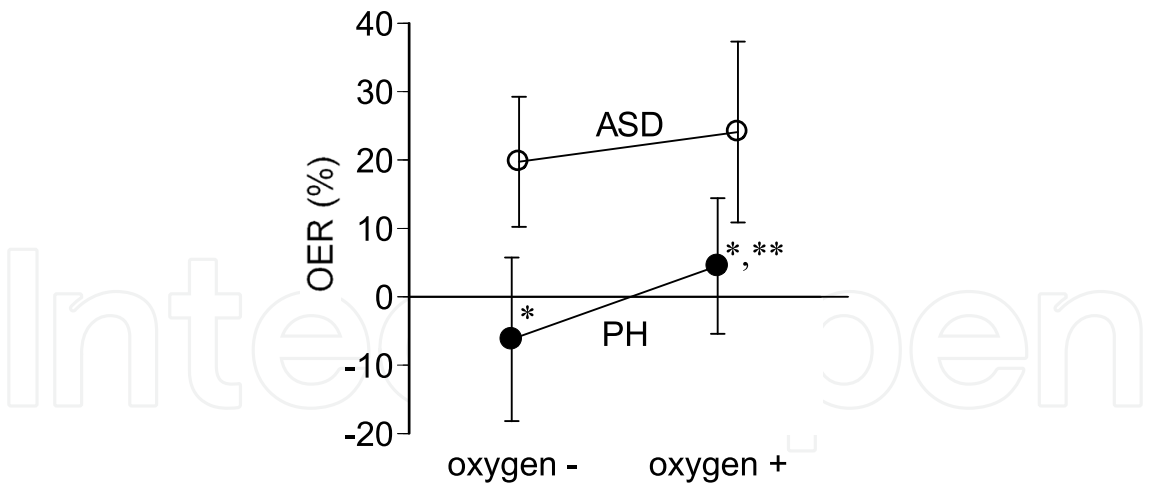
Kobayashi *et al* demonstrated that, in isolated perfused heart, both the intracellular and the perfusate L/P ratio increases at higher cardiac workloads (Kobayashi & Neely, 1979). The L/P ratio of a given cell is thought to reflect the cytosolic NADH/NAD ratio (Rasmussen et al., 2009). Since the coronary venous L/P ratio at rest has been reported around 10 (Friedli 1977), our results suggested that the cytosolic NADH/NAD ratio may be higher in the CHD groups, although statistically not significant, than in KD group at rest (Table 3).

Our results suggested that, under the high potential of fatty acids oxidation, 1) the low level of acceleration of oxidative metabolism as in ASD group resulted in increasing of lactate oxidation for filling NADH because of limitation of glycolysis activity by fatty acids oxidation, 2) the higher level of cardiac work as in PH group results in the faster rates of glycolysis by cellular hypoxia and/or adrenaline (Brooks et al., 2002, Massie et al., 1995), which were also accompanied by increased conversion of pyruvate to lactate by over-production of NADH (Figure 3).



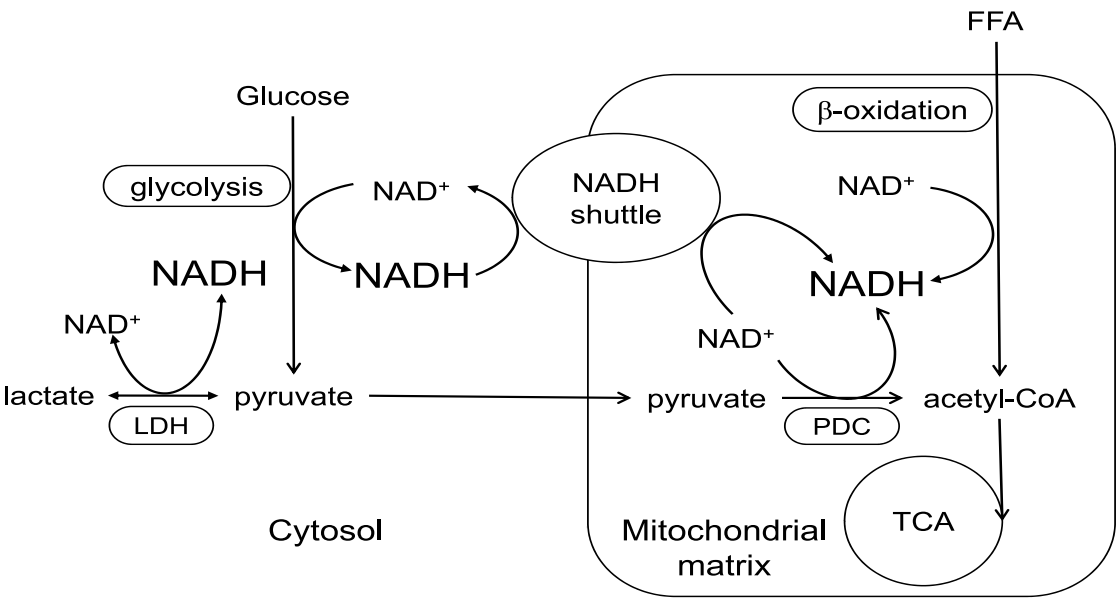
KD, Kawasaki disease; ASD, atrial septal defect; PH, pulmonary hypertension;
*, significantly different from KD; **, significantly different from ASD.

Fig. 1. Myocardial oxygen extraction rate (OER) of glucose, lactate, and fatty acids



ASD, atrial septal defect; PH, pulmonary hypertension.
*, significantly different from ASD; **, significantly different from oxygen -

Fig. 2. Effects of oxygen administration of myocardial lactate use



LDH, lactate dehydrogenase; PDC, pyruvate dehydrogenase complex.
NADH produced by glycolysis or conversion of lactate to pyruvate is carried into the mitochondrial matrix via NADH shuttle. In mitochondrial matrix, NADH is produced from conversion of pyruvate to acetyl-CoA catalyzed by PDC.

Fig. 3. Relationship between myocardial energy substrate use and pathways for oxidation of NADH

	KD	ASD	PH	ANOVA <i>P</i>
Age (year)	3.5±2.3	6.9±3.0	2.1±0.8†	0.005
HR (bpm)	123±24	118±1	129±27	NS
RVPsys (mmHg)	24±4	40±12*	80±22**, †	<0.001
LVPsys (mmHg)	112±15	116±9	100±10	NS
RVP/LVP	0.22±0.05	0.35±0.13	0.79±0.17**,†	<0.001
LV DP (x1000)	13.63±2.06	13.61±1.7	12.95±2.82	NS
RV DP (x1000)	2.94±0.65	4.80±1.94	10.32±3.28**,†	0.001
Qp/Qs	1	1.8±0.2	1.7±0.5	-
Hb(g/dl)	12.5±0.7	13.3±0.7	12.9±0.9	NS

HR, heart rate; RVPsys, systolic right ventricular pressure; LVPsys, systolic left ventricular pressure; DP, double products (=ventricular systolic pressure x heart rate); Qp/Qs, pulmonary-sysytolic flow ratio; Hb, hemoglobin
*, significantly different between KD vs ASD; **, significantly different between KD vs VSD; †, significantly different between ASD vs VSD

Table 1. Patients profiles

	KD	ASD	PH	ANOVA <i>p</i>
Aorta				
O2 sat (%)	97.7±0.5	97.1±0.8	95.1±3.3	NS
Glucose (mmol/L)	4.95±1.07	5.48±0.33	5.17±0.88	NS
lactate (mmol/L)	0.72±0.19	0.83±0.44	0.86±0.36	NS
pyruvate (mmol/L)	0.045±0.023	0.048±0.015	0.092±0.093	NS
FFA (mmol/L)	1.28±0.33	1.41±0.44	1.34±0.3	NS
Coronary sinus				
O2 sat (%)	31.5±4.3	35.2±12.5	32.2±5.6	NS
Glucose (mmol/L)	4.93±1.07	5.46±0.28	5.18±0.95	NS
lactate (mmol/L)	0.53±0.16	0.53±0.3	0.95±0.47**,†	0.033
pyruvate (mmol/L)	0.052±0.027	0.037±0.01	0.1±0.081	NS
FFA (mmol/L)	1.08±0.34	1.2±0.46	1.15±0.3	NS

**, significantly different from ASD group; †, significantly different from ASD group

Table 2. Myocardial substrate uptake

	O2	KD	ASD	PH	ANOVA <i>p</i>
CV L/P	-	11.8±3.3	15.1±8.7	15.6±13.0	NS
	+	11.6±4.3	15.8±6.0	14.0±8.8	NS
Redox potential					
Eh _{cv} (mV)	-	-236.2±4.7	-238.3±7.7	-237.7±8.8	NS
	+	-235.6±6.7	-239.9±5.4	-237.2±7.5	NS
Eh _{ao} (mV)	-	-241.9±7.2	-241.6±5.4	-238.9±9.7	NS
	+	-240.5±6.8	-245.6±4.8	-239.6±6.4	NS
ΔEh (mV)	-	5.7±4.7	3.3±5.9	1.2±4.7	NS
	+	5.0±3.7	5.7±2.7	2.3±4.9	NS

CV, coronary vein; Eh, redox potential, ΔEh, difference of redox potential between artery and coronary vein

Table 3. Anaerobic Metabolism

5. Conclusion

Myocardial energy metabolism in non-cyanotic CHD was basically sustained by fatty acids oxidation whether or not with increasing workloads. The glucose use was accelerated with overload with cellular hypoxia although very variable. Lactate seemed to play an important role to maintain lactate-pyruvate redox potential. When myocardial workloads were mild as in ASD group, the NADH demand was complemented by lactate oxidation. On the other hand, when workloads were as strong as producing a myocardial hypoxic state as in PH group, lactate production was accelerated to maintain the cellular redox state.

6. Acknowledgements

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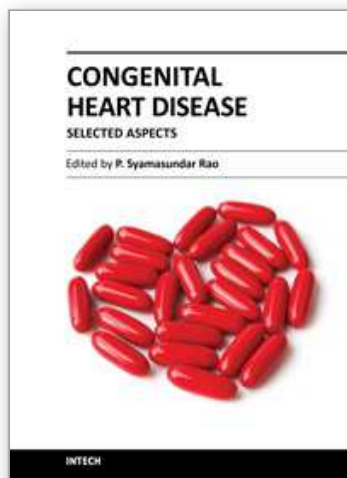
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There are significant advances in the understanding of the molecular mechanisms of cardiac development and the etiology of congenital heart disease (CHD). However, these have not yet evolved to such a degree so as to be useful in preventing CHD at this time. Developments such as early detection of the neonates with serious heart disease and their rapid transport to tertiary care centers, availability of highly sensitive noninvasive diagnostic tools, advances in neonatal care and anesthesia, progress in transcatheter interventional procedures and extension of complicated surgical procedures to the neonate and infant have advanced to such a degree that almost all congenital cardiac defects can be diagnosed and "corrected". Treatment of the majority of acyanotic and simpler cyanotic heart defects with currently available transcatheter and surgical techniques is feasible, effective and safe. The application of staged total cavo-pulmonary connection (Fontan) has markedly improved the long-term outlook of children who have one functioning ventricle. This book, I hope, will serve as a rich source of information to the physician caring for infants, children and adults with CHD which may help them provide optimal care for their patients.

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InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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