Comparison of renal function between cyanotic and acyanotic congenital heart disease in children and adolescent

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A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science Program in Health Development

Faculty of Medicine

Chulalongkorn University

Academic Year 2011

การศึกษาเปรียบเทียบการทำงานของไตระหว่างโรคหัวใจพิการแต่กำเนิดชนิดเขียวและไม่เขียวในผู้ป่วยเด็กและวัยรุ่น

นางสาวยุภาพร อมรชัยเจริญสุข

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาการพัฒนาสุขภาพ
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2554

Thesis title	COMPARISON OF RENAL FUNCTION BETWEEN CYANOTIC AND ACYANOTIC CONGENITAL HEART DISEASE IN CHILDREN AND ADOLESCENT
By	Ms. Yupaporn Amornchaicharoensuk
Field of Study	Health Development
Thesis Advisor	Professor Thewarug Werawatganon,

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ยุภาพร อมรชัยเจริญสุข : การศึกษาเปรียบเทียบการทำงานของไตระหว่างโรคหัวใจพิการแต่กำเนิดชนิดเขียวและไม่เขียวในผู้ป่วยเด็กและวัยรุ่น (COMPARISON OF RENAL FUNCTION BETWEEN CYANOTIC AND ACYANOTIC CONGENITAL HEART DISEASE IN CHILDREN AND ADOLESCENT), อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ศ.นพ.เทวารักษ์ วีระวัฒกานนท์, 36 หน้า

วัตถุประสงค์ : เพื่อศึกษาเปรียบเทียบการทำงานของเนื้อเยื่อไต (glomerular function) และการทำงานของท่อไต(tubular function) และเปรียบเทียบความชุกของการทำงานของไตผิดปกติระหว่างผู้ป่วยโรคหัวใจแต่กำเนิดชนิดเขียว กับชนิดไม่เขียวในผู้ป่วยเด็กและวัยรุ่น

รูปแบบการวิจัย : การวิจัยเชิงวิเคราะห์ ณ จุดเวลาใดเวลาหนึ่ง

สถานที่ทำวิจัย : โรงพยาบาลวชิรพยาบาล โรงพยาบาลพระมงกุฎเกล้า โรงพยาบาลรามาธิบดี

ระเบียบวิธีวิจัย : อาสาสมัครจะได้รับการเจาะเลือด3 ซีซี เพื่อส่งตรวจ CBC, electrolyte, BUN, creatinine, Magnesium และเก็บปัสสาวะ เพื่อส่งไปตรวจ urine NAG และurine creatinine urine sodium, magnesium, protein, microalbumin,

ผลการศึกษา : ผู้ป่วย 46 รายเป็นโรคหัวใจแต่กำเนิดชนิดเขียว 15 ราย ผู้ป่วยโรคหัวใจแต่กำเนิดชนิดไม่เขียว 31 ราย พบมีความแตกต่างอย่างมีนัยสำคัญทางสถิติใน systolic blood pressure, hemoglobin, oxygen saturation, cardiac surgery, functional class ระหว่างผู้ป่วย 2 กลุ่ม ความชุกของการเกิดความผิดปกติในการทำงานของท่อไต (tubular dysfunction) และการทำงานของเนื้อเยื่อไต (glomerular dysfunction) ในผู้ป่วยโรคหัวใจแต่กำเนิดชนิดเขียวมีมากกว่าชนิดไม่เขียว

สรุป: ความชุกของความผิดปกติในการทำงานของหน่วยกรองไต (glomerular dysfunction)และความผิดปกติในการทำงานของท่อไต (tubular dysfunction) ในผู้ป่วยโรคหัวใจแต่กำเนิดชนิดเขียวมีมากกว่าชนิดไม่เขียว การตรวจคัดกรองการทำงานไตทั้งทำงานของหน่วยกรองไตและการทำงานของท่อไตในผู้ป่วยโรคหัวใจแต่กำเนิดชนิดเขียวและไม่เขียว จะเป็นประโยชน์เพื่อช่วยค้นหาความผิดปกติในการทำงานของไตได้แต่เนิ่นๆ

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต.....

ปีการศึกษา 2554 ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก .....

##5374906530 : Major Health Development
KEYWORDS: RENAL DYSFUNCTION, GLOMERULAR DYSFUNCTION, TUBULAR DYSFUNCTION, CYANOTIC CONGENITAL HEART DISEASE, ACYANOTIC CONGENITAL HEART DISEASE

YUPAPORN AMORNCHAICHAROENSUK: COMPARISON OF RENAL FUNCTION BETWEEN CYANOTIC AND ACYANOTIC CONGENITAL HEART DISEASE IN CHILDREN AND ADOLESCENT. ADVISOR: PROFESSOR THEWARUG WERAWATGANON, M.D., 36 pp.,

Objective: To evaluate glomerular and tubular function and compare prevalence of renal dysfunction between cyanotic and acyanotic congenital heart disease in children and adolescent.

Study design: cross-sectional analytic study

Setting: Vajira hospital, Pramongktklao hospital, Ramathibodi hospital

Research methodology: Blood 3 cc was collected from eligible patients both cyanotic and acyanotic congenital heart disease to evaluated for CBC, electrolyte, BUN, creatinine, magnesium. Urine was collected to evaluated for Urine NAG, creatinine, sodium, magnesium, protein, Microalbumin

Results: Forty-six patients, 15 cyanotic and 31 acyanotic congenital heart disease (CHD) were studied. Statistical significant different regarding to systolic blood pressure, hemoglobin, oxygen saturation, cardiac surgery and functional class found between 2 groups. Prevalence of tubular dysfunction and glomerular dysfunction in cyanotic was significantly higher than acyanotic CHD.

Conclusion: The prevalence of glomerular and tubular dysfunction in cyanotic congenital heart was higher than acyanotic congenital heart disease. The screening of both glomerular and tubular function is useful to early detect abnormality of glomerular and tubular function in both cyanotic and acyanotic congenital heart disease.

Field of Study Health Development Student's Signature……..

Academic Year 2011 Advisor's Signature…….

ACKNOWLEDGEMENTS

I would like to express my gratitude to Faculty of Medicine Chulalongkorn University for granted to this study. I am grateful to Professor Thewarug Weerawatganon, my advisor for the helpful advice and comments until this study accomplished. I also wish to thank Assistant Prefessor Chulalak Komoltri for valuable advices. I also appreciate coordinators and subjects at Vajira hospital, Pramongkutklao hospital, Ramathibodi hospital and staff of Department of Biochemistry, Faculty of Medicine, Chulalongkorn University for their cooperation.

In addition, I would like to thank all staffs of Clinical Epidemiology Unit, Faculty of Medicine Chulalongkorn University for their help.

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CHAPTER I

INTRODUCTION

Background and rationale

Patient with congenital heart disease may develop abnormal renal function such as glomerulopathy with proteinuria and impair tubular function. The risk of developing renal impairments is particularly high in patients with cyanotic heart disease [1-2].The incidence of renal abnormalities increase with the degree of cyanosis and may also increase with the duration of cyanosis[3].The test that usually use for assessing renal function such as serum BUN and creatinine are not sufficiently sensitive because these measurements can be in the normal range despite considerable renal function impairment. These tests will become significantly abnormal only after considerable damage to the kidney. Several studies have documented glomerular dysfunction such as proteinuria, decrease renal blood flow and decreased glomerular filtration rate in patient with congenital heart disease only a few studies have discussed renal tubular dysfunction [2,4-5]. Urinary biomarker use to evaluate functional integrity of glomerulus is microalbumin, total protein while other parameter for evaluate tubular function include β 2-microglobulin, retinol binding protein, α1-microglobulin, urinary excretion of Na^+ and NAG (N-acetyl-β-D-glucosaminidase) [6-7]. Fractional excretion of Na^+ and magnesium are used to determine renal tubular dysfunction. β 2-microglobulin is excreted from the blood through the glomeruli into urine and most is reabsorbed from renal tubular cells. Urinary β 2-microglobulin excretion increases in case of renal tubular dysfunction[7]. NAG(N-acetyl-β-D-glucosaminidase) is a lysosomal enzyme derived from membrane surface components of the most vulnerable and damaged proximal tubule epithelium[7-8]. Increased urinary β 2-microglobulin and NAG levels are useful biomarkers to detect tubular dysfunction[7-8]. Most of the previous studies of renal function have been conducted in older children and adults and studied in cyanotic heart disease[1-3]. Most of the congenital heart disease patients in Thailand hardly know their renal function, and could only detect the abnormality when

they admit in the hospital. Some of them have pathological proteinuria and develop nephrotic syndrome. Therefore we interest to study the renal function in both cyanotic and acyanotic congenital heart disease (CHD) in young children and adolescent before they have severe kidney injury. If we detect abnormal renal function early, we could have convince pediatric cardiologists to awareness of renal impairments and avoid nephrotoxic agents in these patients. For the patient who has glomerular injury such as significant proteinuria they should have been follow up at renal clinic to monitor renal function regularly.

CHAPTER II

LITERATURE REVIEW

Literature search strategy

Published original studies in the area of interest were sought and retrieved, initially using several electronic searches, i.e. Pubmed, Ovid and the Cochrane library. The keywords were renal dysfunction, cyanotic congenital heart disease, acyanotic congenital heart disease.

Review and related literature

Renal function represent by estimate glomerular filtration rate (eGFR) and usually estimated from creatinine clearance. The measurement of creatinine clearance by using 24 hr collection of urine is impractical for children. Thus Schwartz formula was used to estimated GFR in children. There were studied that compared the Schwartz- predicted GFR versus measured GFR, the mean differences between estimated and measured GFR ranged from -0.4 to 10 ml/min /1.73 m^2. Measurement of creatinine clearance by 24 hr collection of urine does not improve the estimate of GFR over the Schwartz formula [9].Sensitive marker of tubular injury have been identified in acute and chronic kidney disease. N-acetyl-β-D-glucosaminidase (NAG) is a proximal tubular lysosomal enzyme which is release during damage to proximal tubules. Increased urine NAG can be detected by enzymatic assay in the kidney diseases that involve tubulointerstitial damage. Fractional excretion of sodium and magnesium were used to determine renal tubular dysfunction. Fractional excretion of magnesium ($FEMg^{2+}$) is a sensitive marker for the detection of early tubulointerstitial injury. Futrakul P et al, found that $FEMg^{2+}$ correlates directly with the degree of tubulointerstitial fibrosis[10]. Microalbuminuria is commonly used as an early marker of renal injury due to it often precedes a decline in renal function. Urine protein to creatinine ratio is another test to detect pathological proteinuria but less sensitive than urine microalbumin[11]. From the study by Agras PI, et al[12], 20 children with

acyanotic heart disease, 23 children with cyanotic congenital heart disease (CHD) and 13 healthy children has been investigated for renal tubular function. The median fractional excretion of Na^+ in the cyanotic group (1.3%) and urine NAG / U creatinine ratio 2,648 U/mol were found to be higher when compared to acyanotic group (1.1 %) (2,321 U/mol) but the differences were not statistical significant. Median fractional excretion of Na^+ and urine NAG / U creatinine ratio in the cyanotic CHD group were significantly higher than those in control group ($P < 0.05$). There were no statistical significant difference between acyanotic and cyanotic CHD with respect to urinary β 2-microglobulin / creatinine, urinary albumin / creatinine and glomerular filtration rate (GFR). The ratio of patients with urinary NAG /U creatinine above normal range was significantly higher in the cyanotic group than in control ($p < 0.05$). This study conclude that tubular injury can be detected before glomerular injury and occurs within the first decade of life. Previous studies have emphasized that nephropathy in cyanotic CHD manifests in the second decade of life. Krull, et al[13], studied 27 patients of age range 0-25 years who had cyanotic CHD and found that only 1 of the patients under 10 year had pathological proteinuria whereas 4 patients older than 20 year had this problem. Awad H, et al[14], studied 86 children and were group to 6 groups consisted of 14 children as control group (G1), 72 children with cyanotic CHD were divided according to age from below 1 year to more than 10 year into 4 equal groups each containing 18 patients (G2-5) 10 of 72 patients underwent palliative surgery were defined as G6. This study showed that with increasing duration of cyanosis there was a significant elevation in urinary biomarker of glomerular and proximal tubular function. The patient who underwent palliative surgery had significant decrease excretion of urinary parameters of kidney function such as Urine NAG, Urine microalbumin, Urine protein/creatinine. According to the study by Inatomi J et, al [14], cyanotic nephropathy(CN) defined as the presence of significant proteinuria(spot urine protein to creatinine ratio > 0.25) or renal dysfunction(24 hr creatinine clearance < 80 ml/min/1.73 m^2). This study found that hematocrit levels and filtration fraction were

significant and independent risk factors for the development of cyanotic nephropathy. Hyperviscosity due to polycythemia may be responsible for the development of cyanotic nephropathy. The mechanisms of the development of proteinuria in patients with CN are still unknown, there are several possibilities. First, the hyperviscosity-induced decrease in peritubular capillary blood flow lead to an increase in glomerular capillary pressure resulting in proteinuria. Second hypothesis, marked increase in the glomerular capillary surface area may impair podocyte function resulting in proteinuria. Cyanosis was a strong multivariate predictor of glomerular filtration rate together with functional class and the use of diuretics[15-17]. Dimopoulous K, et al[18], studied prevalence of renal dysfunction in adult patients with congenital heart disease (ACHD) and found that the prevalence of significant renal impairment was 18-fold higher in noncyanotic congenital heart disease (8%) than in the general population and 35-fold higher in cyanotic congenital heart disease (15.8%). Elevated levels of atrial natriuretic peptide, renin, aldosterone and norepinephrine have been reported in ACHD, even when asymptomatic. Deranged cardiac autonomic nervous activity has been described in various ACHD, it is likely that chronic renal hypoperfusion and significant neurohormonal activation contribute to the deterioration of renal function. Chronic hypoxia could affect renal function both directly and through secondary erythrocytosis and increased blood viscosity[19]. Renal dysfunction was related to systemic ventricular dysfunction, promote cardiac remodeling and progression of cardiac dysfunction. The presence of renal dysfunction even mild, appears to be related to adverse outcome among ACHD patients. Therefore periodic screening of renal function in all ACHD patients to obtain prognostic information and identify patients who may benefit from earlier intervention should be encouraged.

CHAPTER III

RESEARCH DESIGN AND METHODOLOGY

Research question

Primary research question

Is abnormal glomerular and tubular function in children and adolescent with cyanotic congenital heart disease more frequent than acyanotic congenital heart disease?

Secondary research question

1.Is prevalence of abnormal tubular function in children and adolescent with cyanotic congenital heart disease more frequent than acyanotic congenital heart disease?

2.Does urinary glomerular marker correlate with tubular marker ?

Objectives

Primary objective

1.To compare glomerular and tubular function between cyanotic and acyanotic congenital heart disease in children and adolescent

Secondary objective

2.1To compare prevalence of abnormal tubular function of cyanotic and acyanotic congenital heart disease in children and adolescent

2.2 To determine correlation between urinary glomerular and tubular marker for kidney injury in children and adolescent with congenital heart disease

Research Hypothesis

Primary objective

Null hypothesis

The glomerular and tubular function in children and adolescent with cyanotic heart disease do not differ from acyanotic congenital heart disease

Alternative hypothesis

The glomerular and tubular function in children and adolescent with cyanotic heart disease differerent from acyanotic congenital heart disease

Secondary objective

Null hypothesis

The prevalence of abnormal tubular function in cyanotic congenital heart disease in children and adolescent do not differ from acyanotic congenital heart disease

Alternative hypothesis

The prevalence of abnormal tubular function in cyanotic congenital heart disease in children and adolescent different from acyanotic congenital heart disease

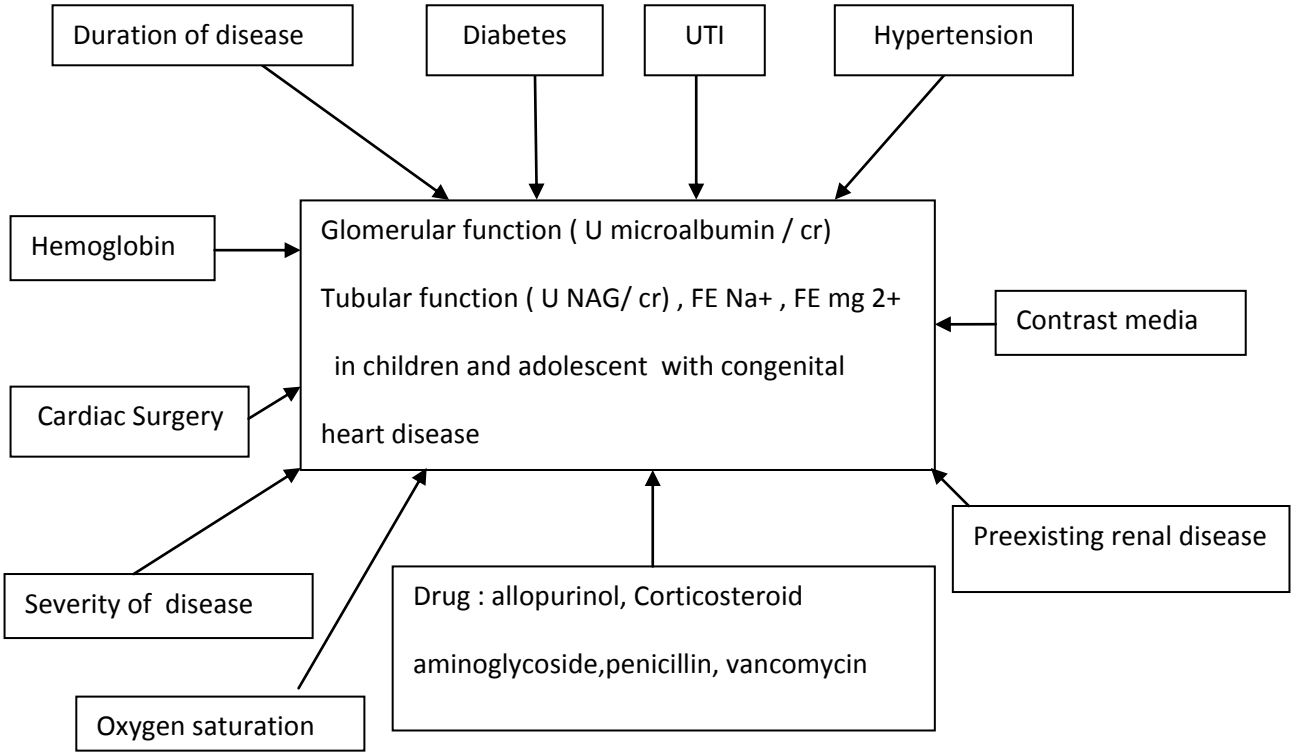
Null hypothesis

There is no correlation between urinary glomerular marker and tubular marker

Alternative hypothesis

There is correlation between urinary glomerular marker and tubular marker

Conceptual framework



Keywords

NAG (N-acetyl-β-D-glucosaminidase), Microalbumin

Fractional excretion of sodium , magnesium

eGFR (estimated glomerular filtration rate)

Renal dysfunction, Cyanotic congenital heart disease

Acyanotic congenital heart disease

Operation definitions

eGFR (estimated glomerular filtration rate) calculated from Schwartz formula[9]

$$eGFR = \frac{\text{Height (cm)} \times \text{constant}}{\text{serum creatinine}}$$

constant values : children and adolescent girls = 0.55

: adolescent boys = 0.7

Definition of renal dysfunction [9]

Normal renal function estimated GFR > 90 ml/min/1.73 m^2

Mild impaired renal function estimated GFR 60-89 ml/min/1.73 m^2

Moderate impaired renal function estimated GFR 30-59 ml/min/1.73 m^2

Spot urine protein / urine creatinine ratio over 0.2 in children older than 2 years old and over 0.5 in children 6-24 month old [9]

Urine NAG(N-acetyl-β-D-glucosaminidase): urinary enzyme derive from membrane surface of damaged proximal tubular epithelium

Urine NAG / urine creatinine > 5.2 Unit /gram creatinine indicate tubular damage[20].

Urine microalbumin /urine creatinine > 30 mg / gram creatinine indicate pathologic albuminuria [21]

Fractional excretion of sodium (FE Na^+): amount of sodium that excrete to urine compared to the amount filter and reabsorbed used determine renal tubular function . FE Na^+ > 1 % indicate abnormal tubular function

Fractional excretion of magnesium (FE Mg^{2+}): amount of magnesium that excrete to urine compared to the amount filter and reabsorbed used determine renal tubular function. FE Mg^{2+} > 2.2 % indicate abnormal tubular function [22]

Congenital heart disease (CHD) is an abnormality in the structure or function of the heart or circulatory system that is present at birth, though it may be discovered later in life

Cyanotic CHD is a defect or group of defects in the structure or function of the heart or the great vessels, present at birth, consisting of abnormal blood flow from the right to the left part of the circulatory system (either at the level of the atria, the ventricles, or the great vessels) result in low oxygen levels in the blood usually with arterial oxygen saturation below 85% causing bluish discoloration of the skin and mucous membranes.

Acyanotic CHD is a congenital heart defects present at birth in which all of the blood returning to the right side of the heart passes through the lungs and pulmonary

vasculature in the normal fashion. The common forms of acyanotic congenital heart defects are those where there is a defect in one of the walls separating the chambers of the heart, or obstruction to one valve or artery.

Research design

This is a cross-sectional analytic study

Research methodology

Population and sample

Target population is children 1 year up to 18 years old with cyanotic and acyanotic congenital heart disease in children and adolescent

Study population or sample is children 1 year up to 18 years old with cyanotic and acyanotic congenital heart disease in children and adolescent who attend or admit at Vajira hospital, Pramongkutklao hospital and Ramathibodi hospital

Inclusion criteria

Children 1 year up to 18 years old with cyanotic and acyanotic congenital heart disease at Vajira hospital, Pramongkutklao hospital and Ramathibodi hospital

Exclusion criteria

UTI (urinary tract infection)

Renal disease

Diabetes

Patient who received contrast media within 48 hrs before enrolled to the study

Patient who taking the following medication with in 3 day before enrolled

: Allopurinol, corticosteroid, Aminoglycosides, Vancomycin, penicillin

Patient who had complete surgical correction

Sample size calculation

Sample size is calculated based on primary objective

Primary objective is to compare glomerular and tubular function in children and adolescent who had cyanotic and acyanotic congenital heart disease

From the study by Awad, et al [11] cyanotic CHD aged at least 1 year old (n=54) had the mean U NAG /Ucreatinine between 76 and 245 (SD of 85-150). Healthy controls (n=14) had mean UNAG of 9 (SD=7.6).

In this study it was estimated that the mean of UNAG in the cyanotic group was about 130 compared to 10 in the acyanotic group. Using a 2-sided type I error of 0.05, 90% power, SD of 115, mean difference of 120 (130 vs. 10), a sample of 16 CCHD and 32 ACHD were required as shown below.

$$n_1 = (1+\frac{1}{r})\left[\frac{(Z_{\alpha/2}+Z_{\beta})SD}{\Delta}\right]^2$$

where

Δ = Mean difference in UNAG between CCHD and ACHD = 120

SD = Standard deviation of UNAG = 115

$1-\beta$ = Power = 0.9

α = Type I error = 0.05 (2-sided)

r = $n_2:n_1 = 2$ (n_1, n_2 = sample size in CCHD and ACHD respectively).

Sampling techniques

Consecutive sampling

Data collection

Type of data collected

1.Baseline (demographic) data

Gender (male, female), Age, birth date, body weight, height, blood pressure(mmHg)

Hemoglobin(g/dl), Serum BUN, creatinine (mg/dl)

Cardiac surgery, oxygen saturation

2.Primary outcome variable

Estimated glomerular filtration rate (eGFR) by Schwartz formula

Fractional excretion of sodium (FE Na^{+}),

Fractional excretion of magnesium (FE Mg^{2+})

Urine protein / urine creatinine (cr)

Urine microalbumin / urine creatinine (cr)

Urine NAG (N-acetyl-β-D-glucosaminidase) / urine creatinine (cr)

3.Secondary outcome variable

Prevalence of abnormal tubular function of cyanotic and acyanotic CHD in children and adolescent

Correlation coefficient between glomerular urinary marker and proximal tubule urinary marker

Method of data collection

Children 1 year up to 18 years old with congenital heart disease who attend or admit at Vajira hospital, Pramongkutklao hospital and Ramathibodi hospital will be enrolled after their parent informed consent and received information of this study. We have collaborate with pediatric cardiologist and biochemist for this study

Timing of data collection

1.Urine and blood will be collected and baseline data will be recorded in Case record form

2.Urine will be collected in 2 separated container, one container will be frozen and kept in refrigerator until it will be sent to test for urine NAG at biochemistry department at Chulalongkorn hospital and the other will be sent to test for urine protein, urine microalbumin, urine creatinine, urine sodium, urine magnesium at Vajira hospital

3.Blood will be sent to test for CBC, serum BUN, creatinine, serum sodium , magnesium

Data analysis

1.Baseline variable (table 1)

Continuous data: age, height, body weight, serum BUN, creatinine, hemoglobin, blood pressure, oxygen saturation

If data is normal distribute it will be presented as mean ± sd and compared between 2 group by independent t-test

If data is not normal distribute it will be presented as median (minimum-maximum) and compared between 2 group by Mann Whitney-U test

level of significant accepted at p value < 0.05

Categorical data: gender, cardiac surgery

Will be presented as frequency (percentage)

Will be compared by chi-square or Fisher's exact test level of significant accepted at p value < 0.05

2.Primary outcome data

glomerular and tubular urinary marker of cyanotic and acyanotic congenital heart disease in children and adolescent

Estimated glomerular filtration rate (eGFR) by Schwartz formula

Fractional excretion of sodium (FE Na^{+})

Fractional excretion of magnesium (FE Mg^{2+})

Urine total protein / urine creatinine

Urine microalbumin / urine creatinine

Urine NAG (N-acetyl-β-D-glucosaminidase) / urine creatinine

If data is normal distribute it will be presented as mean ± sd and compared between 2 group by independent t-test

If data is not normal distribute it will be presented as median (minimum – maximum) and compared between 2 group by Mann Whitney U test

The level of significant accepted at p value < 0.05

3.Secondary outcome data

Prevalence of tubular dysfunction in cyanotic and acyanotic CHD in children and adolescent

Correlation coefficient between proximal tubule urinary marker

(Urine NAG / urine creatinine), FE $Mg^{2+}$and glomerular urinary marker (Urine microalbumin / urine creatinine), (Urine protein /urine creatinine)

If data is normal distribute then Pearson correlation will be used,

If data is not normal distribute then Spearman's correlation will be used

The level of significant accepted at p value < 0.05

Expected benefit and application

1.Determination of glomerular and tubular function in children and adolescent with congenital heart disease. If we found abnormal renal function we would have follow up renal function regularly and give suggestion to avoid nephrotoxic agents and caution for their nutrition that may aggravate the deterioration of renal function such as high salt diet and high purine diet.

2.In case that we found significant proteinuria we will follow up spot urine protein and urine creatinine every 3 to 6 month. If patient have pathological proteinuria we will consider ACE-I or prednisolone to reduce proteinuria.

Detrermination the correlation of urinary tubular marker (urine NAG/ urine creatinine) ,FE $Mg^{2+}$and urinary glomerular marker (urine microalbumin / urine creatinine), (Urine protein/ urine creatinine)

3. and identify these with early abnormal renal function. Due to the urine tubular marker (urine NAG / urine creatinine) is a specific and sensitive test to detect early tubular injury but it cannot done in general hospital .We have to send the test to the special lab at biochemistry department of Chulalongkorn hospital. If we found that this test correlate with urine microalbumin / urine creatinine. We could use urine microalbumin / urine creatinine to predict urine NAG /urine creatinine .

4.Detection CHD with early abnormal renal function allowing early intervention and monitoring renal function more regularly for these patient to slow progression of the chronic kidney disease.

Limitation

The limitation of the study is the time to collect data is not enough to achieving the number of sample in time.

Ethical consideration

The research proposal must be approved by Hospital Ethics Committee before starting the study.There is some intervention in this study such as blood test, but it is low risk for any harm to participants. The data will be kept in a personal computer belongs to the investigator. The entrance to the data will need a specific code. Result of the study will be presented in general, not as individual data. Informed consent is needed. However, the mothers or caregiver can withdraw from the study at any time and still receive the same standard care. There is no conflict of interest in this study.

CHAPTER IV

RESULTS

Demographics and baseline data

Forty-six patients comprising of 15 cyanotic congenital heart disease (CCHD) and thirty-one acyanotic congental heart disease (ACHD) were enrolled in the presented study. There were no statistical significant differences regarding to age, bodyweight, height, diastolic blood pressure, BUN, serum creatinine, estimated glomerular filtration rate, Spot urine microalbumin / urine creatinine and fractional excretion of sodium between cyanotic and acyanotic congenital heart disease. Median of spot urine protein / urine cretinine, urine NAG / urine creatinine and mean of fractional excretion of magnesium were increased in cyanotic congenital heart disease with statistical significant different from acyanotic congental heart disease. Three of fifteen(20%) cyanotic congenital heart disease and seven of thirty-one(22.5%) acyanotic congenital heart disease had mild impaired estimated glomerular filtration rate (eGFR 60-89 ml/min/1.73 m^2). Seven of forty-six (8.69%) patients who had mild impaired estimated glomerular filtration rate age less than ten year old. Thirteen of fifteen (86.6 %) cyanotic congenital heart disease and fifteen of thirty-one (43.38%) acyanotic congenital heart disease had fractional excretion of magnesium over than 2.2 % with statistical differences between them. Median of urine NAG /creatinine in cyanotic group was more than acyanotic congenital heart disease with statistical significant. The prevalence of Urine NAG/ creatinine > 5.2 U /gram creatinine in cyanotic and acyanotic were 46.6 and 9.67% respectively with statistical significant different. There were no statistical significant different in mean of (FE Na^+) and prevalence of FE Na^+ > 1% between two groups.

Seven of fifteen (46.6%) cyanotic congenital heart disease and two of thirty-one (6.45%) acyanotic congenital heart disease had pathological proteinuria with statistical significant differences. There were statistical significant different regarding to median

of urine protein / urine creatinine between two groups. Six of fifteen (40%) cyanotic and three of thirty-one (9.67%) acyanotic congenital heart disease had microalbuminuria, the prevalence between two groups were statistical significant different. Median of spot urine Microalbumin/ creatinine was increased in cyanotic group but there were no statistical significant different between two groups.

Table 1 Characteristics of congenital heart disease

Disease	Number of patient
Acyanotic CHD	
Atrial septal defect (ASD)	13
Ventricular septal defect (VSD)	10
Pulmonary stenosis (PS)	2
TOF S/P BT shunt	1
PS, AR, AV valve regurgitation	1
Mitral valve prolapse	1
PS, PDA	1
Patent ductus arteriosus (PDA)	1
VSD, AR, Tricuspid regurgitation, Coarctation of aorta	1
Cyanotic CHD	
TOF	6
Pulmonary atresia, VSD, MAPCA	2
AV canal defect, PDA, ASD, VSD, PH	1
Complete AV canal defect, PS	1
PA, VSD, Tricuspid atresia	1
VSD with PH	1
DORV with PS	1
Hypoplastic left heart, DORV, AS, PH	1
Unbalanced AV canal defect	1

MAPCA = Major aortopulmonary collateral arteries, DORV = double outlet right ventricle, AS = aortic stenosis

AR = aortic regurgitation, PH = pulmonary hypertension, PS = pulmonary stenosis, PA = pulmonary atresia,

Table 2 summary of demographic and baseline data of two groups

	Mean ± SD or Number (%)		
	Cyanotic CHD (n=15)	**Acyanotic CHD (n=31)**	**P-value**
Age (years)	9.33 ± 5.56	7 ± 3.5	0.153
Body weight (kg)	25.5 ± 15.37	21.7 ± 8.54	0.387
Height (cm)	119.8 ± 27	116.9 ±18.4	0.666
Systolic blood pressure (mmHg)	94.7 ±9.97	106.9 ±16.31	0.011*
Diastolic blood pressure (mmHg)	58.87 ± 10.46	57.35 ± 10.10	0.64
Hemoglobin (g/dl)	17.88 ± 4.43	12.01 ± 1.23	0.000*
Oxygen saturation (%)	75.7 ± 11.21	97 ± 2.32	0.000*
Cardiac surgery (palliative)	9 (60)	4 (12.9)	0.001*
Functional class			
Class I	2 (13.3)	30 (96.77)	0.000*
Class II	9 (60)	1 (3.22)	
Class III	3 (20)	0	
Class IV	1 (6.66)	0	

Table 3 Medication usage in Congenital heart disease

Medication	Cyanotic CHD	Acyanotic CHD
No medication	4	14
Digoxin	0	15
Aspirin	3	0
Digoxin, furosemide, beroprost	2	0
Enaril ,aspirin, furosemide, aldactone	1	0
Aspirin, propanolol	1	0
Digoxin, furosemide, aspirin, aldactone	1	0
Digoxin, enaril, beroprost	1	0
Digoxin, furosemide, aldactone	0	1
Enaril, aspirin	1	0
Metoprolol	1	1

Table 4 Prevalence of glomerular and tubular dysfunction

	Number (%)		
	Cyanotic CHD (n=15)	**Acyanotic CHD (n=31)**	**P-value**
Estimated GFR (ml/min/1.73 m^2)			
Normal (GFR> 90)	11(73.33)	24(77.4)	
Mild decrease(GFR 60-89)	3 (20)	7 (22.5)	0.503
Moderate decrease (GFR 30-59)	1 (6.66)	0	
Urine protein / urine creatinine (>0.2)	7 (46.6)	2(6.45)	0.003*
Urine microalbumin /urine creatinine (> 30 milligram / gram)	6 (40)	3(9.67)	0.042*
Urine NAG /urine creatinine (> 5.2 Unit/ gram creatinine)	7 (46.6)	3(9.67)	0.008*
Fractional excretion of sodium > 1%	6 (40)	12(38.71)	0.585
Fractional excretion of magnesium > 2.2%	13(86.6)	15 (48.38)	0.02*

Data presented are number (%) , * p - value < 0.05

Table 5 Biochemical data of cyanotic and acyanotic congenital heart disease

	Mean ± SD or Median (min – max)		
	Cyanotic CHD (n=15)	**Acyanotic CHD (n=31)**	**P-value**
BUN (mg/dl)	16.58 ±11.5	11.81 ±3.1	0.135
Serum creatinine (mg/dl)	0.68 ±0.32	0.61± 0.18	0.363
Estimated GFR (ml/min/1.73 m2)	117.04 ± 37.18	113.98 ± 34.05	0.783
Fractional excretion of sodium %	0.86 ± 0.75	0.92 ± 0.63	0.780
Fractional excretion of magnesium %	5.03 ± 3.61	2.48 ± 1.8	0.019*
U NAG / creatinine (Unit/gram creatinine)	3.59 (0 - 32)	1.64(0 - 29.3)	0.008**
Urine protein / creatinine	0.16(0.075-10.78)	0.08(0.02-0.5)	0.001**
Urine microalbumin / creatinine (milligram /gram)	20.6 (0.22 - 5102.75)	10.45 (1.4 - 206.25)	0.073

* p - value < 0.05 using independent t-test

** p - value < 0.05 using Mann-Whitney U test

Table 6 Correlation coefficient (r) between urine glomerular and tubular marker in Congenital heart disease

	U NAG / Ucr	FE Mg^{2+}
Urine Microalbumin / U creatinine	0.273	0.095
Urine protein / U creatinine	0.375*	0.373*

CHAPTER V

DISCUSSION

The present study demonstrated both glomerular and tubular dysfunction among cyanotic and acyanotic congenital heart disease age range 1 -18 years old. The prevalence of mild impaired estimated glomerular filtration rate (eGFR) were found in both cyanotic and acyanotic congenital heart disease with no statistical significant different. Several previous studied conducted in cyanotic congenital heart disease and enrolled older children than the present study. The author's found that prevalence of mild impaired eGFR in acyanotic congenital heart disease (22.58 %) was higher than cyanotic congenital heart disease (21.7%) but no statistical significant. The possible cause of mild impaired eGFR in acyanotic CHD may be hemodynamic change from transient congestive heart failure and renal hypoperfusion. The mean of systolic blood pressure in cyanotic CHD was lower than acyanotic CHD may be due to medication usage such as angiotensin converting enzyme and diuretics in cyanotic CHD. Tubular dysfunction represented by fractional excretion of sodium (FE Na^{+}) > 1 % or fractional excretion of magnesium (FE Mg^{2+}) > 2.2 % or urine NAG/ urine creatinine > 5.2 U / gram creatinine. Fractional excretion of sodium (FE Na^{+}) used to screening tubular function. Fractional excretion of magnesium is useful to screening tubulointerstitial disease. There is a linear correlation between FE $Mg^{2+}$and peritubular capillary flow which supports the chronic ischemic inducing altered tubular function and tubulointerstitial fibrosis[22]. Urine NAG (N-acetyl-beta-D-glucosaminidase) is a high molecular weight proximal tubular lysosomal enzyme which is released during damage to proximal tubules. Increased urine level of NAG can be detected in tubulointerstitial damage[23-24].

The results of the present study were different from the other studies regarding to high prevalence of renal tubular dysfunction (mild impaired e GFR, FE Na^{+} >1%, FE Mg^{2+}>2.2%) in acyanotic congenital heart disease which was more than expectation. Agras et al, studied 20 cyanotic and 23 acyanotic congenital heart disease

and found lower eGFR in cyanotic congenital heart disease but mean GFR between 2 groups were not statistically significant, there were also no statistical significant differences regarding to median fractional excretion of sodium and Urine NAG / U creatinine between cyanotic and acyanotic congenital heart disease. The authors found more tubular dysfunction especially prevalence of FE Mg^{2+} > 2.2 % and Urine NAG / urine creatinine > 5.2Unit /gram creatinine in cyanotic group than acyanotic congenital heart disease with statistical significant .There were no statistical significant different between two groups regarding to prevalence of FE Na^{+} > 1 %. The present study showed that FE Mg^{2+} > 2.2 % was more sensitive to detected tubular dysfunction than urine NAG/urine creatinine and more practical to use to screening for tubular function.

Glomerular dysfunction represented by spot urine protein/urine creatinine > 0.2 or urine microalbumin/ urine creatinine over 30 microgram / milligram. Spot urine protein/urine creatinine > 0.2 indicated pathological proteinuria, microalbuminuria is used as early marker of renal injury due to it often precedes a decline in renal function[9].

Accordind to studied of Krull et al [10], 27 cyanotic congenital heart disease age 0-25 years old found only 1 patient under 10 years old had pathological proteinuria. The present study showed more prevalence of glomerular dysfunction regarding to spot urine protein/ urine creatinine > 0.2 in cyanotic (46.6%) than acyanotic (6.45%) congenital heart disease with statistical significance. Three of fifteen (20%) with cyanotic congenital heart disease age less than 10 year old had pathological proteinuria. The authors found that the prevalence of microalbuminuria was higher in cyanotic than acyanotic congenital heart disease with statistically significant but median level of urine microalbumin/urine creatinine between two groups were not statistical significant different. The results in the present study showed high prevalence of mild renal impairment in acyanotic congenital heart disease especially tubular dysfunction can detected more than glomerular dysfunction. There were moderate correlation between

urine protein /urine creatinine and urine NAG/urine creatinine with correlation coefficient (r) = 0.375 and correlation coefficient (r) between urine protein/urine creatinine and FEMg $^{2+}$ = 0.373 with statistical significant. Therefore we may use urine protein /urine creatinine to predict urine NAG/ urine creatine and FE Mg $^{2+}$.But There were no correlation between urine microalbumin/ urine creatinine and Urine NAG/urine creatinine and FE Mg $^{2+}$.The mechanisms of renal dysfunction in cyanotic congenital heart disease causes by several factors such as chronic hypoxia, low cardiac output, elevated hematocrit, duration of cyanosis, severity of the disease. Low cardiac output due to left ventricular dysfunction cause poor perfusion to vital organs especially kidneys. Progressive renal dysfunction from low cardiac output result from poor renal perfusion and increase renal vasoconstriction mediated by neurohormonal and autonomic activation[19].For acyanotic congenital heart disease, the mechanisms of renal dysfunction in unknown due to few studied conducted in this group. Further study should be done to evaluate risk factors of renal dysfunction in acyanotic congenital heart disease. The study by Dimopoulos K et al[19], showed that renal dysfunction was related to systemic ventricular dysfunction. Renal dysfunction can promote cardiac remodeling and progression of cardiac dysfunction through loss of sodium and volume overload. The screening of renal function in the congenital heart disease is useful to prevent and delay the deterioration of renal function.

CHAPTER VI

CONCLUSION

The prevalence of glomerular and tubular dysfunction in cyanotic congenital heart was higher than acyanotic congenital heart disease. In the present study showed high prevalence of renal dysfunction especially tubular dysfunction in acyanotic congenital heart disease. The screening of tubular function by using fractional excretion of magnesium is useful to early detect abnormality of tubular function. For glomerular function screening , using spot urine protein / urine creatinine and urine microalbumin / creatinine to detect early pathological proteinuria and early intervention such as ACE-I prescription and avoid nephrotoxic agents would be benefit and delay deterioration of renal function.

RECOMMENDATION

Further study about intervention for abnormal glomerular dysfunction in cyanotic congenital heart disease with proteinuria by using angiotensin converting enzyme inhibitor should be conducted.

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APPENDICES

Appendix A

Informed consent form

(ใบยินยอมเข้าร่วมการวิจัย)

การวิจัยเรื่อง การศึกษาเปรียบเทียบการทำงานของไตระหว่างโรคหัวใจแต่กำเนิดชนิดเขียวและไม่เขียวในผู้ป่วยเด็กและวัยรุ่น

ก่อนที่จะลงนามในใบยินยอมให้บุตรของข้าพเจ้าเข้าร่วมในการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายถึงวัตถุประสงค์ของการวิจัย ขั้นตอนการวิจัย อาการข้างเคียงที่อาจเกิดขึ้นจากการวิจัย รวมทั้งประโยชน์ที่จะเกิดจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว

ผู้วิจัยรับรองว่าจะตอบคำถามต่างๆที่ข้าพเจ้าสงสัยด้วยความเต็มใจ ไม่ปิดบังซ่อนเร้นจนข้าพเจ้าพอใจ

การให้คำยินยอมให้บุตรของข้าพเจ้าเข้าร่วมในการศึกษานี้ เป็นไปโดยสมัครใจ ข้าพเจ้ามีสิทธิที่จะบอกเลิกการเข้าร่วมในการวิจัยนี้ของบุตรข้าพเจ้าเมื่อใดก็ได้ และการบอกเลิกการเข้าร่วมในการวิจัยนี้จะไม่กระทบต่อการดูแลรักษาที่บุตรข้าพเจ้าพึงจะได้รับจากแพทย์

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะที่เกี่ยวกับบุตรของข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะในรูปที่เป็นผลสรุปการวิจัย การเปิดเผยข้อมูลเกี่ยวกับบุตรของข้าพเจ้าตจ่อหน่วยงานต่างๆที่เกี่ยวข้องกระทำได้เฉพาะกรณีจำเป็น ด้วยเหตุผลทางวิชาการเท่านั้น

ผู้วิจัยรับรองว่า หากเกิดภาวะแทรกซ้อนใดๆแก่บุตรของข้าพเจ้าจากการวิจัยดังกล่าว บุตรของข้าพเจ้าจะได้รับการรักษาพยาบาลและดูแลอย่างใกล้ชิดโดยไม่คิดมูลค่า

ข้าพเจ้าได้อ่านข้อความดังข้างต้นแล้ว มีความเข้าใจดีทุกประการ และได้ลงนามยินยอมในใบยินยอมนี้ด้วยความเต็มใจ

ลงนาม…….

(……)

ผู้ปกครอง/ ผู้อุปการะโดยชอบด้วยกฎหมาย

วันให้คำยินยอม วันที่……เดือน……พ.ศ……

ลงนาม……พยาน

(……)

ลงนาม……ผู้ทำวิจัย

(……)

Appendix B

Patient information sheet

ข้อมูลสำหรับผู้ป่วยและผู้ปกครอง

การศึกษาทางคลินิก การวิจัยเรื่อง การศึกษาเปรียบเทียบการทำงานของไตระหว่างโรคหัวใจแต่กำเนิดชนิด เขียวและไม่เขียวในผู้ป่วยเด็กและวัยรุ่น

เรียนท่านผู้ปกครอง

เหตุผลของการวิจัย

ผู้ป่วยที่เป็นโรคหัวใจแต่กำเนิดอาจมีการทำงานของไตผิดปกติเช่น มีโปรตีนรั่วในปัสสาวะ การทำงานของท่อไตผิดปกติ โดยความเสี่ยงในการเกิดความผิดปกติดังกล่าวมักจะพบในโรคหัวใจพิการแต่กำเนิดชนิดเขียวได้มากกว่าชนิดไม่เขียว ความผิดปกติของการทำงานของท่อไต จะตรวจพบได้ก่อนความผิดปกติในการทำงานของเนื้อเยื่อไต โดยจะตรวจพบได้ภายในอายุ 10 ปี ในประเทศไทยผู้ป่วยกลุ่มนี้ปกติจะไม่ได้รับการตรวจการทำงานของไต แพทย์จะตรวจเมื่อคนไข้มานอนโรงพยาบาลเพื่อรอการสวนหัวใจ หรือไม่สบาย และการตรวจการทำงานของไตตามปกติมักไม่มีความไวพอเพียงที่จะตรวจพบความผิดปกติที่มีในระยะแรกๆได้ ผู้ป่วยบางรายจะถูกส่งมาปรึกษากุมารแพทย์โรคไตเมื่อมีความผิดปกติมากแล้ว เช่น มี โปรตีนรั่วในปัสสาวะปริมาณมาก การทำงานของไตลดลง

การวิจัยนี้จึงมีวัตถุประสงค์ที่จะศึกษาเปรียบเทียบหาความผิดปกติในการทำงานของไตในผู้ป่วยเด็กและวัยรุ่น ที่มีโรคหัวใจแต่กำเนิดชนิดเขียวและไม่เขียว โดยใช้การตรวจที่มีความไวในการค้นหาความผิดปกติในการทำงานของไตได้แต่เนิ่นๆ เพื่อที่จะหาทางป้องกันและรักษาความผิดปกติในการทำงานของไตก่อนที่จะเกิดภาวะไตเสื่อมจนนำไปสู่ไตวายเรื้อรังในอนาคต นอกจากนี้จะทำให้ทราบถึงความชุกของความผิดปกติในการทำงานของไตในผู้ป่วยโรคหัวใจแต่กำเนิดชนิดเขียวและไม่เขียว และเป็นข้อมูลสำคัญในการพิจารณาวางแนวทางในการดูแลรักษาผู้ป่วยให้ดียิ่งขึ้น เนื่องจากหากเราตรวจพบเจอความผิดปกติในผู้ป่วยรายใด แพทย์ผู้ดูแลจะได้คอยเฝ้าระวังหลีกเลี่ยงการให้ยาหรือ สารทึบแสงที่จะเป็นพิษต่อไต และติดตามการทำงานของไตอย่างสม่ำเสมอ แนะนำการรับประทานอาหารและการปฏิบัติตัวแก่ผู้ป่วยเพื่อชะลอการเสื่อมของไต

ขั้นตอนการทำวิจัย

1. แพทย์จะทำการซักประวัติ ตรวจร่างกาย ที่ห้องตรวจโรคผู้ป่วยนอก หรือในหอผู้ป่วยกรณีผู้ป่วยใน
2. สำหรับผู้ป่วยที่มารับการตรวจที่ห้องตรวจโรคผู้ป่วยนอก แพทย์จะขอเจาะเลือดผู้ป่วยปริมาณไม่เกิน 3 ซีซี (เทียบเท่ากับครึ่งช้อนชา) และเก็บปัสสาวะเพื่อรอส่งตรวจทางห้องปฏิบัติการ

ในกรณีที่เป็นผู้ป่วยในผู้วิจัยจะขอแบ่งเลือดจากการตรวจเลือดตามปกติโดยไม่ได้ทำให้ผู้ป่วยเจ็บเพิ่มขึ้นแต่อย่างใด

3.หากผลการตรวจของผู้ป่วยมีความผิดปกติ ผู้วิจัยจะแจ้งให้ผู้ป่วยทราบในการนัดตรวจครั้งต่อไป โดยจะให้คำแนะนำการดูแลสุขภาพและให้ยาหากมีความผิดปกติ เช่น ตรวจพบมีโปรตีนรั่วในปัสสาวะหรือมีความดันโลหิตสูง และจะนัดผู้ป่วยมาตรวจการทำงานของไตอย่างสม่ำเสมอ

สิ่งที่ควรทราบ หากท่านยินยอมให้บุตรของท่านเข้าร่วมโครงการวิจัยนี้

1.ท่านไม่ต้องเสียค่าใช้จ่ายในการตรวจเลือดและปัสสาวะ ในการเข้าร่วมในการวิจัยครั้งนี้

2.การให้คำยินยอมให้บุตรของท่านเข้าร่วมในการวิจัยนี้ เป็นไปโดยสมัครใจ ท่านอาจปฏิเสธที่จะให้บุตรของท่านเข้าร่วม หรือขอถอนตัวจากการศึกษานี้ได้ทุกเมื่อ โดยไม่กระทบต่อการดูแลรักษาที่บุตรของท่านจะได้รับการรักษาจากแพทย์

3. ผู้วิจัยยินดีตอบคำถามต่างๆที่ท่านสงสัยโดยละเอียด ตลอดเวลาการวิจัย

4. ผลการวิจัย จะใช้สำหรับวัตถุประสงค์ทางวิชาการเท่านั้น การเปิดเผยทำได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย ข้อมูลต่างๆของผู้ป่วยจะถูกเก็บเป็นความลับ ไม่มีการเปิดเผยต่อสาธารณชน ขอรับรองว่าจะไม่มีการเปิดเผยชื่อของท่านหรือบุตรของท่านโดยเด็ดขาด

5. ท่านอาจจะไม่ได้รับประโยชน์จากการเข้าร่วมโครงการวิจัย

หากท่านมีปัญหาหรือข้อสงสัยประการใด กรุณาติดต่อ

แพทย์หญิง ยุภาพร อมรชัยเจริญสุข กุมารแพทย์โรคไต
ภาควิชากุมารเวชศาสตร์ ตึกมหาวชิราวุธชั้น 9
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โทรศัพท์ 0-2244-3156 หรือมือถือ 08-9141-1300

ผู้วิจัยขอขอบคุณในความร่วมมือของท่านมา ณ ที่นี้

Appendix C

Participant no. ☐☐☐

Case record form for renal function in children and adolescent with congenital heart disease

Birth date (date /month/year) ☐☐/☐☐/☐☐☐☐

Sex ☐ 1 male ☐ 2 female

Diagnosis ☐ 1 cyanotic heart disease ☐ 2 Acyanotic heart disease

Disease……..

Echocardiogram……

Cardiac surgery ☐ 1 yes ☐ 2 no

Type of surgery……

Oxygen saturation……

Severity of disease (Modified Ross Heart failure)

Class 1 ☐ Asymtomatic

Class 2 ☐ mild tachypnea or diaphoresis with feeding in infants. Dyspnea on exertion in older child

Class 3 ☐ marked tachypnea or diaphoresis with feeding in infants. Marked dyspnea on exertion,Prolonged feeding time with growth failure

Class 4 ☐ Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

Participant no. ☐☐☐

Medication

……

……

Body weight ☐☐☐.☐ kilogram

Height ☐☐☐.☐ cm

Blood pressure : Systolic pressure ☐☐☐ diastolic pressure ☐☐☐

Serum Bun mg/dl ☐☐☐

Serum creatinine ☐.☐☐ mg/dl

Serum Magnesium ☐☐.☐ mg/dl

Serum sodium Na^+ ☐☐☐ mEq/l

Serum K^+ ☐.☐☐ mEq/l

Serum Cl^- ☐☐☐☐ mEq/l

Serum CO_2 ☐☐ ☐ mEq/l

CBC : Hemoglobin ☐☐. ☐ gm/dl

Urine specific gravity ☐.☐☐☐

Urine blood……

Urine glucose……

Participant no. | | | |

Urine WBC ……cell / HPF

Urine RBC……..cell / HPF

Urine Na +mEq/l | | | |

Urine Mg 2+ | | | | mEq/l

Urine protein | | | | mg/dl

Urine microalbumin | | | |

Urine NAG | | | |

Urine creatinine | | | |

eGFR $\frac{(\text{Kx L})}{\text{Pcr}}$ | | | |

K values

Low birth weight during first year of life = 0.33

Term newborn during first year of life = 0.45

Children and adolescent girls = 0.55

Adolescent boys = 0.7

L = height (cm)

P cr = plasma creatinine

Participant no. ☐☐☐

$FE\ Na^{+} = \left(\frac{U\ Na^{+} \times P\ cr}{P\ Na^{+} \times U\ cr} \right) \times 100\ \%$ ☐☐☐

$FE\ Mg^{2+} = \left(\frac{U\ Mg^{2+} \times P\ cr}{0.7 \times P\ Mg^{2+} \times Ucr} \right) \times 100\ \%$ ☐☐☐

Spot Urine protein / urine creatinine ☐☐☐

Urine microalbumin / urine creatinine ☐☐☐

Urine NAG /urine creatinine ☐☐☐

VITAE

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Publications

2009	Prevalence of childhood hypertension and association between hypertension and obesity in secondary school students