厚生労働科学研究費補助金

難治性疾患等政策研究事業

肺動脈低形成症候群の病態解明、管理、治療に関する研究

平成27年度　総括研究報告書

研究代表者　中　西　敏　雄

平成28(2016)年3月

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Ⅰ 総括研究報告

厚生労働科学研究費補助金(難治性疾患等政策研究事業)
総括研究報告書

肺動脈低形成症候群の病態解明、管理、治療に関する研究

研究代表者　中西敏雄
東京女子医科大学循環器小児科

研究要旨

肺動脈低形成症候群は、主肺動脈が無いか極めて低形成で、主要体肺側副血管、肺動脈低形成、多発性末梢性肺動脈狭窄を含み、発症原因は不明である。本研究の目的は、肺動脈低形成症候群の患者を登録し、病態把握、自然歴の把握、手術法と手術時期、予後に関するデータ分析を多施設共同で組織的、体系的に行うことである。

術後20年の長期生存率は、肺動脈閉鎖＋心室中隔欠損＋主要体肺側副血管群では７１％であったのに比し、肺動脈閉鎖＋心室中隔欠損群では８６％であり、肺動脈閉鎖＋心室中隔欠損＋主要体肺側副血管群の方が、術後20年までの生存曲線は有意に低かった。肺動脈閉鎖＋心室中隔欠損＋主要体肺側副血管群では幼児期-小児期に肺動脈のuniforcalizationが76例においてなされ、8例は手術不能であった。小児期新生児期手術の生存者のうち、49例でRastelli手術が施行された。手術死亡は8%であった。主肺動脈を認めた61例の20年生存率は84%であったのに対し、主肺動脈を認めなかった23例の20年生存率は50%にすぎなかった。

次いで、単心室血行動態疾患について、肺動脈低形成症候群の遠隔期Quolity of lifeを調べた。肺動脈低形成症候群で、三尖弁閉鎖や肺動脈弁閉鎖では、新生児期の短絡術についで、乳児期にはグレン手術が施行され、グレン手術生存者では、１－２歳でフォンタン手術が施行されていた。フォンタン手術到達は全体の 80%にすぎなかった。高度の蛋白漏出性胃腸症に罹患した患者も 3%に存在した。肺動脈低形成のためにグレン手術でとどまっている患者の QOL は特に悪いことがわかった。

肺動脈低形成症候群に於いては肺動脈末梢狭窄に対してカテーテル治療も施行されるが、その成功率は　５０−７０％で低い結果であった。

今回の研究では、肺動脈低形成症候群の予後は不良であることがわかった。このデータにもとづいて、治療指針の作成が可能である。指針が作成されれば、本疾患を持つこどもや成人にとって最適な治療法、管理法が施され、疾患克服のために大きく寄与することができる。長期的にも、難病指定などの指針に用いることができる。ひいては小児、成人の医療、保健のレベルの向上につながるものである。

[背景]

肺動脈低形成症候群は、主肺動脈が無いか極めて低形成で、主要体肺側副血管、肺動脈低形成、多発性末梢性肺動脈狭窄を含む。多くは心奇形を合併し、ファロー四徴症、三尖弁閉鎖症、肺動脈閉鎖症、右室低形成症候群、総動脈幹症などが合併することがある。チアノーゼなど多様な臨床症状を呈する原因不明の症候群である。生命予後に深く関わる肺血管疾患に対して、新生児期から個々の症例に適した治療、管理計画を立て、生涯にわたって、臨床症状に基づいた生活指導や治療を続ける必要がある。最良の治療方法は未確立で、病態、最適な手術の組み合わせ、手術時期、手術のリスク、術後の予後について、今までに大規模な調査は行われてこなかった。

[研究目的]

本研究の目的は、肺動脈低形成症候群の患者を登録し、病態把握、自然歴の把握、手術法と手術時期、予後に関するデータ分析を多施設共同で組織的、体系的に行うことである。各施設で行われた手術の成績を検討し、リスクを調べ、心不全治療の有効性を検討する。

[研究方法]

後方視的研究：調査票（資料）を作成し、分担研究者施設において、過去 10 年間のケーススタディーを行った。肺動脈低形成症候群の小児の病歴簿を調べ、病態、心奇形の組み合わせ、手術法、手術成績、予後、合併奇形の頻度、全身症状の種類と頻度を調べた。患者数は、80 人であった。生命予後に深く関わる心血管疾患について、主な心血管疾患の症状、大動脈や肺動脈の太さ、その形態、などについて、各施設からのデータの集積を行った。

[研究体制]

我が国の本症候群患者を診療している主要施設による多施設共同の疫学研究を行った。研究分担者は、所属する施設の本疾患群の患者を登録し、病態、心奇形の組み合わせ、手術法、手術成績、予後、合併奇形の頻度、全身症状の種類と頻度などに関するデータを収集した。研究代表者は全データベースの構築を行い分析した。

[倫理面への配慮]

倫理審査委員会の承認の基に、臨床研究に関する倫理指針に基づき研究を行った。

[平成26年度の研究成果]

肺動脈低形成症候群で肺動脈閉鎖＋心室中隔欠損＋主要体肺側副血管の65例、対照として肺動脈閉鎖＋心室中隔欠損の89例の集計を行った。心疾患の合併を100%の例に認め、心室中隔欠損、肺動脈弁狭窄、肺動脈閉鎖、肺動脈低形成を合併していた。

術後20年の長期生存率は、肺動脈閉鎖＋心室中隔欠損＋主要体肺側副血管群では７１%であったのに比し、肺動脈閉鎖＋心室中隔欠損群では８６%であり、肺動脈閉鎖＋心室中隔欠損＋主要体肺側副血管群の方が、術後20年までの生存曲線は有意に低かった。

肺動脈閉鎖＋心室中隔欠損＋主要体肺側副血管群では幼児期-小児期に肺動脈のuniforcalizationが76例においてなされ、8例は手術不能であった。小児期新生児期手術の生存者のうち、49例でRastelli手術が施行された。手術死亡は8%であった。主肺動脈を認めた61例の20年生存率は84%であったのに対し、主肺動脈を認めなかった23例の20年生存率は50%にすぎなかった。

次いで、単心室血行動態疾患について、肺動脈低形成症候群の遠隔期Quolity of lifeを調べた。肺動脈低形成症候群で、三尖弁閉鎖や肺動脈弁閉鎖では、新生児期の短絡術についで、乳児期にはグレン手術が施行され、グレン手術生存者では、１-２歳でフォンタン手術が施行されていた。フォンタン手術到達は全体の80%にすぎなかった。高度の蛋白漏出性胃腸症に罹患した患者も3%に存在した。肺動脈低形成のためにグレン手術でとどまっている患者のQOLは特に悪いことがわかった。

肺動脈低形成症候群に於いては肺動脈末梢狭窄に対してカテーテル治療も施行されるが、その成功率は　５０-７０%で低い結果であった。

[成果の活用・提供]

今回の研究では、肺動脈低形成症候

群に於いては肺動脈末梢狭窄に対してカテーテル治療も施行されるが、その成功の予後は不良であることがわかった。遠隔期成績は、肺動脈低形成例で悪く、肺動脈が無い例では 10 年で５０%の死亡率であった。このデータにもとづいて、治療指針の作成が可能である。指針が作成されれば、本疾患を持つこどもや成人にとって最適な治療法、管理法が施され、疾患克服のために大きく寄与することができる。長期的にも、難病指定などの指針に用いることができる。ひいては小児、成人の医療、保健のレベルの向上につながるものである。

[文献]

Evidence for palliative enlargement of the right ventricular outflow tract in severe tetralogy of Fallot.
Korbmacher B, Heusch A, Sunderdiek U, Gams E, Rammos S, Langenbach MR, Schipke JD.
Eur J Cardiothorac Surg. 2005 Jun;27(6):945-8.

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Suzuki Y, Ikeda Y, Hisagi M, Nakayama S.
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Pulmonary atresia with ventricular septal defect, extremely hypoplastic pulmonary arteries, major aorto-pulmonary collaterals.
Metras D, Chetaille P, Kreitmann B, Fraisse A, Ghez O, Riberi A.
Eur J Cardiothorac Surg. 2001 Sep;20(3):590-6; discussion 596-7.

健康危険情報

なし

知的財産権の出願、登録状況

特許取得

なし

実用新案登録

なし

その他

なし

研究者名	分担した研究項目	研究実施場所　（機関）	研究実施期間	代表・分担
中西敏雄	総括・企画	東京女子医科大学	H27.4.1～H28.3.31	代表
朴　仁三	後方視的研究（データ収集と解析）	榊原記念病院	H27.4.1～H28.3.31	分担
小野　博	後方視的研究（データ収集と解析）	国立成育医療センター	H27.4.1～H28.3.31	分担
小野安生	後方視的研究（データ収集と解析）	静岡県立こども病院	H27.4.1～H28.3.31	分担
白石　公	後方視的研究（データ収集と解析）	国立循環器病センター	H27.4.1～H28.3.31	分担
山岸敬幸	後方視的研究（データ収集と解析）	慶應義塾大学	H27.4.1～H28.3.31	分担
大月審一	後方視的研究（データ収集と解析）	岡山大学	H27.4.1～H28.3.31	分担

平成26年度難治性疾患政策研究事業
肺動脈低形成症候群の病態解明、管理、治療に関する研究調査票

調査年月日
共同研究者
施設名

肺動脈低形成症候群の疫学
肺動脈低形成症候群とは診断時のPA Indexが100未満の状態と定義する。
肺動脈分枝が存在しない主要体肺側副血管の場合、側副血管の太さに関係なく、本症に入れて下さい

患者ID
性別
生年月日 年 月 日
年齢 歳
診断日 年 月 日
診断時年齢
現在 死亡年月日 年 月 日

012疾患名
□ファロー四徴症 □肺動脈閉鎖症 □総動脈幹症 □両大血管右室
□三尖弁閉鎖症 □右室低形成症候群 □大血管転換症 □その他...

合併心内異常（該当するものを全て選ぶ）
□心室中隔欠損 □肺動脈弁狭窄 □肺動脈閉鎖 □主要体肺側副血管

染色体異常
□Alagille症候群 □Williams症候群 □その他...
□22q11.2欠失症候群 □不明

家族内発症

カテーテル施行日

カテーテル施行日1回目 年 月 日 PA index
カテーテル施行日2回目 年 月 日 PA index
カテーテル施行日3回目 年 月 日 PA index

手術

姑息術有無

姑息術1回目施行日 年 月 日 種類
姑息術2回目施行日 年 月 日 種類
姑息術3回目施行日 年 月 日 種類

平成26年度難治性疾患政策研究事業
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肺動脈低形成症候群の疫学
肺動脈低形成症候群とは診断時のPA Indexが100未満の状態と定義する。
肺動脈分枝が存在しない主要体肺側副血管の場合、側副血管の太さに関係なく、本症に入れて下さい

心内手術有無 □
心内手術施行日 □□ 年 □ 月 □ 日
心内手術種類 □心内修復術 □Rastelli □Fontan □その他...

カテーテル治療有無 □

術後の心臓後遺症（今回調査時の状態）

チアノーゼ □ SPO2 □ (%)
肺動脈狭窄（右室—肺動脈圧較差20mmHg以上） □
房室弁逆流（2度以上） □
肺動脈弁逆流（2度以上） □
大動脈弁逆流（2度以上） □
肺高血圧（平均圧25mmHg以上） □
体心室収縮障害（駆出率５０％以下） □
肺心室収縮障害（駆出率５０％以下） □
不整脈 □
NYHA □

心臓以外の合併症、後遺症（今回調査時の状態）

発達遅延（IQ 70 以下） □
蛋白漏出性胃腸症 □
慢性肝障害 □肝線維症 □肝硬変 □肝癌 □なし
慢性腎障害（腎機能低下を認める） □

Ⅱ 参考資料

J THORAC CARDIOVASC SURG 88:610-619, 1984

A new method for the quantitative standardization of cross-sectional areas of the pulmonary arteries in congenital heart diseases with decreased pulmonary blood flow

A new angiographic method for quantitative standardization of cross-sectional area of bilateral pulmonary arteries, the PA-index, and retrospective analysis of the PA-index in different types of operative procedures are presented. This study included 40 subjects in the normal control group, 46 patients in the tetralogy group, 26 patients in the Rastelli group, and 15 patients in the Fontan group. The normal value of the PA-index was 330 ± 30 mm²/BSA and was consistent in a wide range of body surface areas from infancy to adolescence. The PA-index in the tetralogy and Rastelli groups ranged from 100 to 400 mm²/BSA. There were no early deaths in the tetralogy group, but the incidence of low cardiac output was higher in patients with a smaller PA-index, especially when the PA-index was less than 150 mm²/BSA. Low cardiac output was more severe in the Rastelli group. The operative mortality was significantly affected by the PA-index. In the Rastelli group, all of the patients with a PA-index of less than 200 mm²/BSA died, whereas the mortality rate in patients with a PA-index of more than 200 was only 6% ($p < 0.01$). The mortality rate was not influenced by any other factors, such as aortic cross-clamp time or age at operation. In the Fontan group, two patients with a PA-index of less than 250 mm²/BSA died of severe heart failure, and 12 of 13 patients with a PA-index of more than 250 survived ($p < 0.01$). Our results indicated the validity of the PA-index in predicting the postoperative prognosis of the various entities. In tetralogy, all patients with a PA-index over 100 mm²/BSA can undergo correction safely; in Rastelli operation, those with a PA-index under 200 should have a palliative procedure first, whereas those with a PA-index over 250 can be considered good candidates for the Fontal procedure. The PA-index may also serve a useful guide in comparing surgical results from different institutions with patients having anomalies of varying severity.

Seisuke Nakata, M.D., Yasuharu Imai, M.D., Yoshinori Takanashi, M.D., Hiromi Kurosawa, M.D., Kitsuhiro Tezuka, M.D., Makoto Nakazawa, M.D., Masahiko Ando, M.D., and Atsuyoshi Takao, M.D., *Tokyo, Japan*

With the advent of cardioplegia and standardization of surgical procedures, recent surgical results for complex cardiac anomalies have been steadily improving. However, the indication for total correction in patients with decreased pulmonary blood flow has been determined rather empirically. Although various methods to estimate the size of the pulmonary artery have been proposed, mainly for the tetralogy of Fallot,[1-3] none can be applied universally for anomalies with decreased pulmonary blood flow.

We have developed a quantitative method to estimate the cross-sectional areas of both pulmonary arteries divided by the body surface area for standardization, and we have applied the resulting value retrospectively to our series of total correction of various anomalies with decreased pulmonary flow.

The purpose of this communication is to present a new angiographic method for estimation of the size of

From the Departments of Cardiovascular Surgery and Pediatrics, The Heart Institute of Japan, Tokyo Women's Medical College, Tokyo 162, Japan.

Received for publication Sept. 19, 1983.

Accepted for publication Dec. 27, 1983.

Address for reprints: Seisuke Nakata, M.D., Department of Cardiovascular Surgery, The Heart Institute, Japan, Tokyo Women's Medical College, 10 Kawada-cho, Shinjuku, Tokyo 162, Japan.

Table I. *Normal values of PA-index*

No.	Age (yr), sex	Diagnosis	BSA (m^2)	RVP (mm Hg)	PAP (m) (mm Hg)	PA-index (mm^2/BSA)	PA area (mm^2)
1	½, F	Prolonged Q-T interval	0.33	30/0	22/10 (13.5)	334	110
2	½, M	Vascular ring	0.33	30/0	24/9 (16)	307	101
3	½, M	WPW	0.35	30/0	25/11 (16)	320	112
4	½, M	H-V block	0.38	–	–	320	122
5	½, M	Funnel chest	0.36	30/0	25/10 (17)	318	114
6	2, F	PS	0.45	48/0	20/8 (13)	395	178
7	2, M	Noonan syndrome	0.53	47/1	18/5 (11)	350	186
8	2, M	MCLS	0.44	–	–	357	157
9	2, M	MCLS	0.56	–	–	310	174
10	3, F	PS	0.58	50/0	20/6 (12)	318	184
11	3, M	MCLS	0.74	–	–	378	280
12	4, M	PS	0.55	50/0	20/7 (14)	388	213
13	4, M	Noonan syndrome	0.67	40/0	25/10 (17.5)	338	223
14	4, M	PS	0.62	–	–	320	198
15	5, M	PS	0.62	45/–2	15/5 (9.5	321	199
16	5, M	MCLS	0.77	–	26/18 (21)	300	231
17	5, M	AV block	0.74	32/3	28/9 (15)	302	223
18	5, F	Funnel chest	0.78	–	–	305	238
19	5, M	SVAS	0.71	26.2	25.11 (19)	315	224
20	5, M	SVAS	0.72	27/2	24.10 (17)	298	215
21	5, F	PS	0.82	48/2	25/12 (16)	320	262
22	6, M	Funnel chest	0.90	24/0	15/8 (12)	302	272
23	6, M	Funnel chest	0.72	24/2	23/11 (15)	320	230
24	6, M	SVAS	0.69	35.0	26/9 (15)	357	246
25	6, F	SVAS	0.69	24/2	26/11 (20)	299	206
26	6, M	AV block	0.81	–	–	345	279
27	7, F	PS	0.85	30/0	18/10 (15)	298	253
28	7, F	AV block	0.90	–	–	330	297
29	8, F	AV block	0.90	21.0	16/6 (11)	318	286
30	8, M	RV tumor	0.81	–	–	324	262
31	8, F	PS	0.87	31/3	18/10 (12)	313	272
32	9, F	SSS	0.96	28/2	(15.5)	369	354
33	9, M	PS	0.93	48/2	25/12 (17)	302	281
34	10, M	MCLS	1.09	–	–	324	353
35	11, M	PS	1.34	47/2	31/14 (21)	310	415
36	12, M	Pigeon chest	1.12	–	–	316	354
37	12, M	MCLS	1.20	–	–	387	464
38	14, M	Funnel chest	1.57	30/3	27/10 (17)	347	545
39	16, F	MCLS	1.42	–	–	377	535
40	17, M	Funnel chest	1.25	–	–	315	394

Legend: BSA, Body surface area. RVP, Right ventricular pressure. PAP, Pulmonary artery pressure. PA area: (l-PA area + r-PA area)/2. WPW, Wolff-Parkinson-White syndrome. H-V, His bundle-ventricular. PS, Pulmonary stenosis. MCLS, Mucocutaneus lymph node syndrome. AV, Atrioventricular. SVAS, Supravalvular aortic stenosis. RV, Right ventricular. SSS, Sick sinus syndrome. MCLS without cardiac lesion, abnormal electrocardiographic findings and without positive angiographic findings; supravalvular aortic stenosis without any pulmonary stenosis; and mild pulmonary stenosis in which peak systolic pressure in right ventricle was less than 50 mm Hg without poststenotic dilatation were included.

the pulmonary arteries (the PA-index) and a retrospective analysis of this PA-index in various procedures including conventional repair of tetralogy of Fallot, extracardiac conduit repair for complex cardiac anomalies, and Fontan procedure for tricuspid atresia and single ventricle. This study reveals that surgical death and heart failure are observed more frequently in patients with underdeveloped pulmonary arteries. We believe that the PA-index may serve to predict the postoperative prognosis in these various procedures.

Patients and methods

Patients were subdivided into four groups: normal controls, tetralogy of Fallot, Rastelli group, and patients undergoing the Fontan procedure.

Normal controls. This group consisted of 40 patients ranging in age from 3 months to 17 years. Twenty-eight were male and 12 female. Body surface areas ranged from 0.33 to 1.57 m^2 (Table I). Patients for the normal control group were selected from our catheterization files and included those either without cardiac lesions or

Table II. *Surgical groups*

	No. of patients	*Age (yr)*	*Palliation*
Tetralogy of Fallot			
Transannular patch	26	4.0 ± 1.5	B-T, 5
Subannular patch	14	4.2 ± 1.6	Waterston, 2
Muscle resection	6	3.6 ± 1.6	
Rastelli			
Pseudotruncus	12	10.5 ± 4.1	B-T, 8; Brock, 1
TGA	10	9.8 ± 3.9	B-T, 4; Waterston, 1
DORV	4	8.5 ± 7.7	B-T, 1; Waterston, 1
Fontan			
Tricuspid atresia	12	9.8 ± 3.6	B-T, 9; Glenn, 1
Single ventricle	1	6	–
DORV with hypoplastic RV	1	9	–
Pulmonary atresia with IVS	1	6	Waterston, Brock

Legend: B-T, Blalock-Taussig shunt. TGA, Transposition of great arteries. DORV, Double-outlet right ventricle. RV, Right ventricle. IVS, Intact ventricular septum.

Table III. *Operative risk factors in the Rastelli group*

	Died	*Survived*	*Significance*
No.	6	19	
Age	7.8 ± 4.7	9.8 ± 4.1	NS
PA-index (mm^2/BSA)	129 ± 33	291 ± 84	$p < 0.01$
Percent of normal	0.39	0.88	
Aortic cross-clamp time	60.8 ± 3.6	66.9 ± 19.3	NS
ECC time (min)	164 ± 46	165 ± 58	NS

Legend: Normal value of PA-index = 330 ± 30 mm^2/BSA. ECC, Extracorporeal circulation. NS, Not significant.

with minimal findings but having normal pulmonary development. The diagnostic categories are listed in Table I. The values of the PA-index in this group serve as control.

Tetralogy of Fallot. Forty-six patients operated upon between February, 1981, and December, 1981, were included. Six had conventional infundibular resection, and 40 had right ventricular outflow reconstruction, 26 with a transannular patch and 14 with a subannular patch. Seven of the 46 patients had undergone previous palliative procedures including a Blalock-Taussig shunt in five and Waterston shunt in two. The ages of the patients ranged from 1 year, 9 months to 9 years (Table II).

Rastelli group. Twenty-six patients were studied in this group. Twelve patients with tetralogy and pulmonary atresia, 10 patients with transposition and pulmonary stenosis or atresia, and four patients with double-outlet right ventricle and pulmonary stenosis or atresia underwent the Rastelli procedure (extracardiac valved-conduit repair) between 1975 and 1982 at our institution. The ages of the patients ranged from 1 to 16 years. Fifteen patients had had previous palliative procedures done, including the Blalock-Taussig shunt in 12 patients, Waterston shunt in one patient, Brock procedure in one, and both Blalock-Taussig and Waterston shunts in one (Table II).

The length of perfusion time with extracorporeal circulation and aortic cross-clamping time is shown in Table III.

Fontan group. In this group there were 12 with tricuspid atresia, two with single ventricle, and one with pulmonary atresia and intact ventricular septum. Of these 15 patients having the Fontan procedure, 14 had direct anastomosis between the right atrial appendage and the pulmonary artery, and one had a nonvalved conduit from the right atrium to the right ventricle (Table II). These operations were performed between 1975 and 1982 at our institution. The ages of the patients ranged from 1 to 18 years. Previous palliative procedures performed in 11 patients included Blalock-Taussig, Glenn, Waterston, and Brock procedures.

All operations were performed with extracorporeal circulation, moderate hypothermia, and a moderate perfusion flow rate. Myocardial protection was accomplished during chemical cardiac arrest induced by Young's solution and cardioplegic solution, consisting of dextrose, insulin, and potassium, and topical cooling with iced saline. The techniques used in each procedure were basically the same in each group.

Measurement of the PA-index. All patients were reviewed either on a cineangiogram or on an anteroposterior angiocardiogram by measuring the diameters of both the right and left pulmonary arteries immediately proximal to the origin of the first lobar branches. Generally, the size of the pulmonary arteries changes in one cardiac cycle. Then, the diameters that were

neasured at the maximum and minimum were averaged in order to obtain a mean diameter for each ndividual. The measurements were repeated by two of is independently. In some patients with previous palliation, such as Blalock-Taussig shunt, aneurysmal segnental dilatation was found in the pulmonary artery. In uch cases, the diameter was measured immediately listal to the aneurysmal dilatation. The cross-sectional irea of each pulmonary artery was calculated as follows:

$$\text{Cross-sectional area (mm}^2) = \pi(\text{diameter}/2f)^2$$

ınd the PA-index as follows:

$$\text{PA-index (mm}^2/\text{BSA}) = (\text{r-PA area} + \text{l-PA area})/\text{BSA}$$

*v*here f is the corrective coefficient for angiographic nagnification, BSA is the body surface area in square neters, the diameter is expressed in millimeters, and the irea is expressed in square millimeters (Fig. 1).

Several examples of the measurement are shown in Fig. 2. The patient whose angiogram is shown on the left had a PA-index of 107 mm²/BSA, the one in the *middle* ıngiogram had a PA-index of 164, and the one on the *right* had a PA-index of 324 (Fig. 2). For the PA-index to be measured, it is mandatory to obtain a clear picture of bilateral pulmonary arteries. In the case of nonconfluent pulmonary arteries, pulmonary venous wedge angiograms has to be employed, as in the *middle panel* in Fig. 3.

Analysis of postoperative course. Values of the PA-index in the normal group were collected from patients of various ages with a wide range of body surface areas; these figures served as the control. In the surgical cases, the postoperative courses were reviewed and compared with the values of the preoperative PA-index. In the latest series of 21 patients with tetralogy of Fallot, the cardiac index was periodically measured in the intensive care unit by the thermodilution method during the first 48 hours after intracardiac repair. In cases of hospital death, the causes were carefully determined from the clinical records and autopsy data.

Statistics. The experimental data were summarized as a mean ± the standard deviation. Student's paired or unpaired t tests were used where appropriate, and the level of significance was derived from a standard table of the t distribution. Selected comparisons between various groups were made by Fisher's exact test. All correlation coefficients were derived by the Pearson method.

Results

PA-index in normal group. The hemodynamic data and PA-index are listed in Table I. This group also

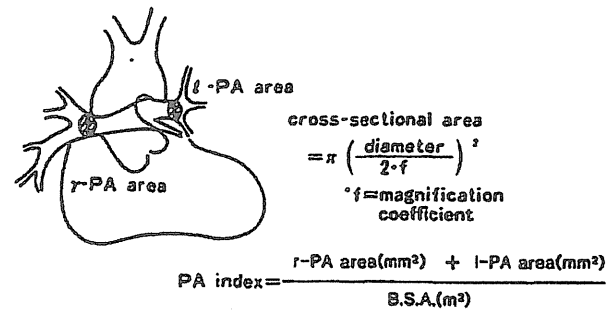

Fig. 1. Illustrations of the measurement of PA-index. The cross-sectional area of both pulmonary arteries was calculated either on a cineangiogram or on an anteroposterior angiocardiogram by measuring diameters of the bilateral pulmonary arteries immediately proximal to the origin of the first branches. After correction for magnification, the sum of both cross-sectional areas was divided by the body surface area. This PA-index was calculated in square millimeters per square meter of body surface area.

included mild pulmonary stenosis with right ventricular pressure lower than 50 mm Hg. The range of body surface areas was between 0.33 and 1.57 m². The sum of cross-sectional areas of both the right and left pulmonary arteries (mm²) was plotted against the body surface area (m²) and the linear regression line was calculated (Fig. 4). The equation is:

$$Y = 343.7X - 10.9$$

where Y = pulmonary area and X = body surface area ($r = 0.98$, $p < 0.01$). In consequence, PA-index could be recognized constant over a wide range of body surface areas from 0.33 to 1.57 m². The PA-index in normal control subjects fell into a range between 300 and 300 with a mean of 330 ± 30 mm²/BSA. These values were considered to be a normal PA-index (Fig. 5).

Distribution of the PA-index in tetralogy of Fallot, Rastelli, and Fontan groups (Fig. 6). In the tetralogy group, the PA-indexes were observed between 100 and 400 mm²/BSA. The PA-index of 100 represented approximately 30% of the control value and 400 could be recognized within the normal range. Ten patients, who corresponded to 20% of patients in the tetralogy group, had a PA-index in the control range, and 40 patients (80%) had a smaller PA-index than the control. In most cases (60% of patients in the tetralogy group), the PA-index was between 150 (45% of normal) and 250 mm²/BSA (75% of normal).

In the Rastelli group, the PA-indexes scattered and the variation was similar to that of the tetralogy group. In this group, the lowest value of the PA-index was below 100 mm²/BSA and smaller than that of the

Fig. 2. Measurement of PA-index in three patients with tetralogy of Fallot. *Left,* A 5-year-old girl with a PA-index of 107 mm²/BSA before operation. *Middle,* A 4-year-old girl with a PA-index of 164 mm²/BSA before operation. *Right,* A 6-year-old boy with a PA-index of 324 mm²/BSA before operation.

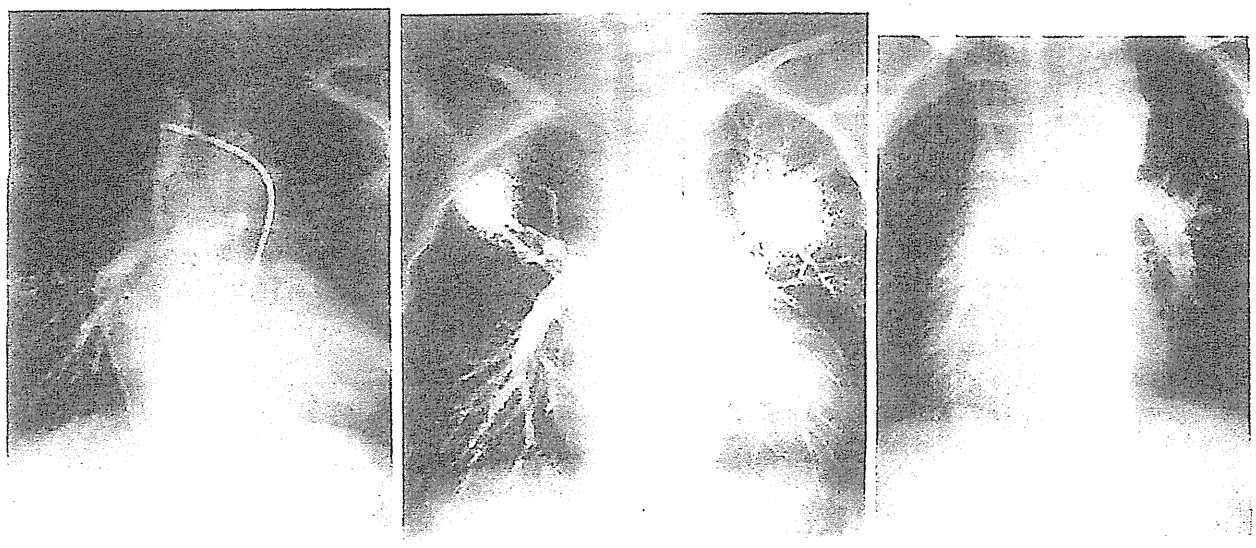

Fig. 3. Angiograms of patients who underwent the Rastelli operation. *Left,* A 14-year-old girl with pseudotruncus and a PA-index of 94 mm²/BSA. *Middle,* A 7-year-old girl with transposition, a nonconfluent pulmonary artery, and a PA-index of 177 mm²/BSA. The picture was reconstituted from two separate wedge angiograms. *Right,* A 5-year-old boy with transposition and a PA-index of 330 mm²/BSA before operation.

tetralogy group. The PA-index in patients with tetralogy of Fallot and pulmonary atresia did not show any significant difference compared to the group with transposition of the great arteries and pulmonary stenosis or atresia ($p < 0.01$). Six patients (25%) had a PA-index in the control range.

In the Fontan group, the PA-indexes were distributed at higher levels than those of the other two entities. All patients had a PA-index of more than 200 mm²/BSA. Eleven patients (70%) had a PA-index in the control range.

Postoperative courses were reviewed with special interest in occurrence and severity of heart failure in relation to the properative PA-index. Here, heart failure

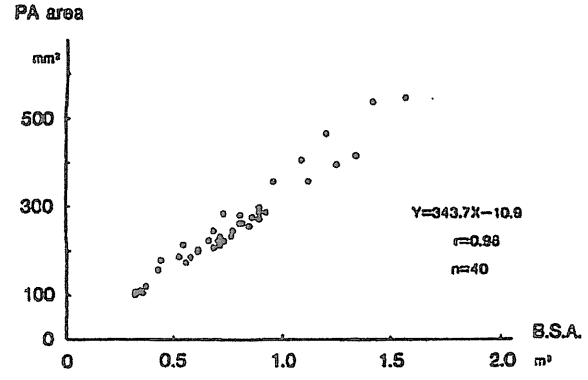

Fig. 4. Correlation between body surface area (*B.S.A.*, in square meters) and summed cross-sectional areas (in square millimeters) of both right and left pulmonary arteries. $Y = 343.7X - 10.9$, $r = 0.98$, $p < 0.01$. The size of the pulmonary arteries changes in one cardiac cycle. The pulmonary arterial *(PA)* areas which are calculated at the maximum and minimum are averaged in order to obtain a mean area for each individual. The PA area represents the sum of right and left pulmonary arterial areas.

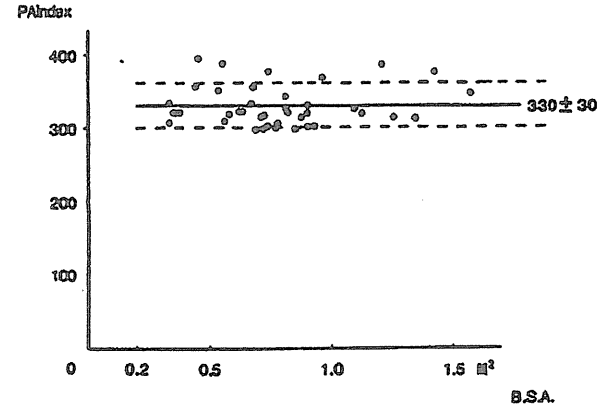

Fig. 5. Normal value of PA-index. Normal values for control were obtained from 40 cases. The values of the PA-index were distributed evenly over a wide range of body surface areas *(B.S.A.)* from 0.33 to 1.57 m^2. The mean value and standard deviation was 330 ± 30 mm^2/BSA.

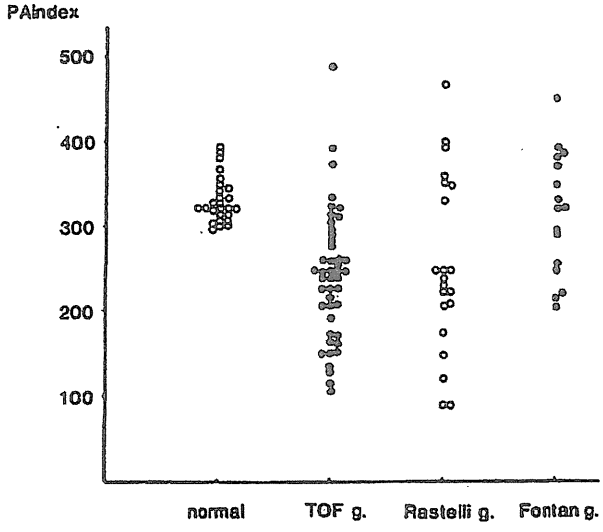

Fig. 6. Distribution of the PA-index before operation in each group. In the control group, the PA-index of all patients falls in a range between 300 and 400 mm^2/BSA. In the tetralogy *(TOF)* and Rastelli groups, the PA-index ranged from 100 to 400 mm^2/BSA. In the tetralogy group, 20% had a normal PA-index, while the remaining 80% showed various degrees of hypoplasia of the pulmonary arteries. In the Fontan group, the development of the pulmonary arteries was better than that in other two groups, and 70% of the patients had a PA-index in the almost normal range.

was graded as either severe, in which the patients needed catecholamine support for more than 72 hours, or moderate, in which the patients required catecholamine support for more than 12 hours and less than 72 hours.

In the tetralogy group, there were no hospital deaths. Ten patients had a PA-index of less than 180 mm^2/BSA, and all of them had severe heart failure, necessitating catecholamine support for more than 72 hours after operation. The mean dosage of catecholamines, of which isoproterenol was considered most appropriate for cyanotic heart disease,[4] was 2.5×10^{-6} mg/kg/min. Out of 15 patients with a PA-index between 180 and 250 mm^2/BSA, six needed catecholamines for more than 72 hours. The mean dosage in these six patients was 0.8×10^{-6} mg/kg/min. Three of these six patients needed catecholamine support because of considerable bradycardia without any sign of heart failure, whereas the remaining nine patients had no sign of heart failure without the aid of an inotropic agent.

Nineteen patients with the PA-index of more than 250 mm^2/BSA had a smooth postoperative course without inotropic support. In the patients with a higher PA-index, the need for inotropic support decreased significantly ($p < 0.01$) (Fig. 7). A similar relationship was noticed between the PA-index and the cardiac index after the repair (Fig. 8). The equation is:

$$Y = 0.0048X + 2.01$$

where X = PA-index and Y = cardiac index ($n = 21$, $r = 0.69$, $p < 0.01$). In six patients with a small PA-index below 200 mm^2/BSA, the cardiac index was measured during catecholamine support.

In the Rastelli group, all the patients with a PA-index less than 200 died. By contrast, the majority rate in

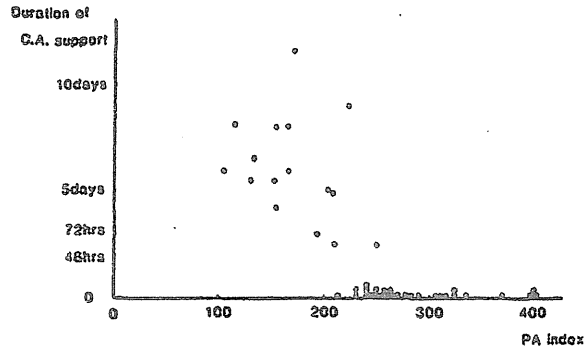

Fig. 7. Occurrence and grade of heart failure following total correction of tetralogy of Fallot. The PA-index before operation and the duration of catecholamine support after total correction of tetralogy is presented. Those with a PA-index of less than 200 mm²/BSA, or less than 60% of normal, tended to have moderate to severe low cardiac output, for which catecholamine support was necessary for more than 72 hours. For patients with a PA-index of 250 mm²/BSA or more, no inotropic support was required after operation. *C.A.*, Catecholamine.

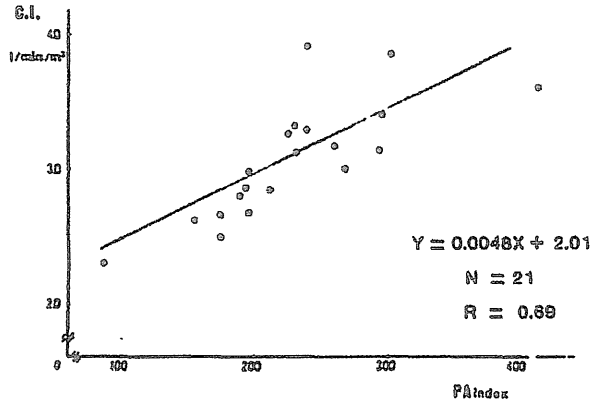

Fig. 8. Correlation between the preoperative PA-index and the cardiac index *(C.I.)* measured 24 hours after operation. $Y = 0.0048X + 2.01$, $r = 0.69$, $p < 0.01$. Those with a PA-index over 250 mm²/BSA had a cardiac index of more than 3.0 without the aid of an inotropic agent.

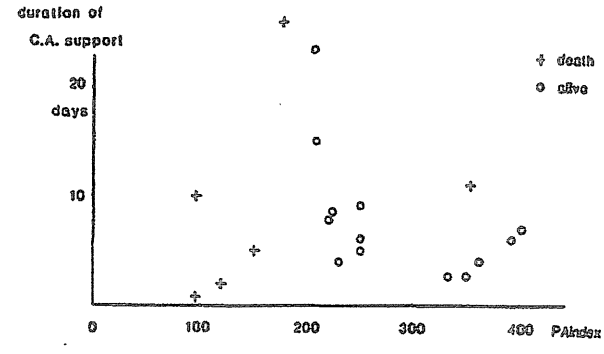

Fig. 9. Mortality after the Rastelli operation in relation to the preoperative PA-index. Retrospective analysis of the PA-index revealed clear-cut evidence as to the lower limit of operability in our hands. All patients with a PA-index of under 200 mm²/BSA died of low cardiac output. However, of the 21 patients who had a PA-index of more than 200 mm²/BSA, only one died (of bronchial bleeding) resulting in a mortality rate of 5% ($p < 0.01$).

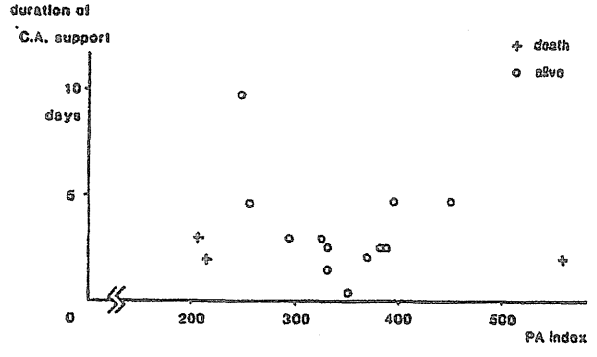

Fig. 10. Mortality after the Fontan operation in relation to the preoperative PA-index. In the 15 patients having Fontan procedures, all but two had a PA-index of more than 250 mm²/BSA, or more than 75% of normal. Two patients with a PA-index under 250 died of low cardiac output soon after the operation. On the other hand, in the group of 13 with a PA-index of more the 250, only one died of ventricular tachycardia. *C.A.*, Catecholamine.

patients with a PA-index of more than 200 mm²/BSA was only 6% (Fig. 9).

The operative mortality rate was not influenced by any other factors, such as the age at operation, the length of perfusion time, and the aortic cross-clamp time (Table III). Six patients died in this series. Three of these six patients had severe heart failure and failed to respond to inotropic support. The other two patients, basically with severe heart failure, died of infection and hepatic dysfunction, respectively. The last patient, with a PA-index of 354 mm²/BSA, died of massive tracheal hemorrhage and severe hypoxia on the eleventh day after a Rastelli procedure. However, his hemodynamic status had been stable without any inotropic agent.

In the Fontan group, patients with a PA-index of more than 300 mm²/BSA had fairly good postoperative hemodynamics with catecholamine support for 2 or 3 days, whereas two patients with a PA-index of less than 250 mm²/BSA died of severe heart failure. These PA-indexes were calculated as 218 and 208, respectively. Unfortunately, one patient with a PA-index above

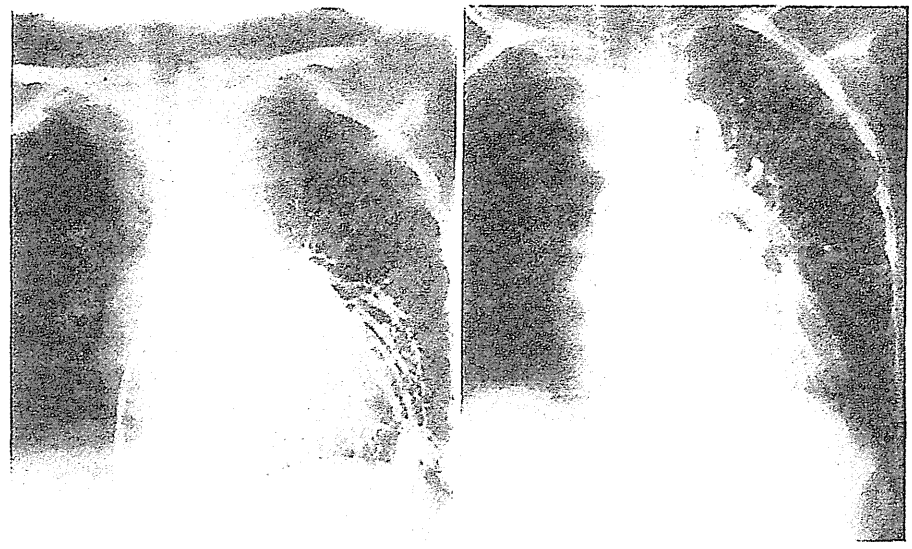

Fig. 11. Increase in PA-index after palliative procedure. Palliation has to be considered to develop a hypoplastic left pulmonary artery like that on the left. Following the left Blalock-Taussig shunt, the PA-index increased from 80 to 150 mm²/BSA in 4 years. However, the patient died of bleeding in the upper gastrointestinal tract after the Rastelli operation. In retrospect, another shunt operation had to be performed on the right side in view of our current lower limit for the PA-index of 200 mm²/BSA for the Rastelli procedure.

the normal range died of uncontrollable ventricular tachycardia in the operating room (Fig. 10).

Discussion

In cyanotic heart disease, the magnitude of the pulmonary blood flow is reflected in the development of the pulmonary arteries[5,6] and the left ventricular volume.[7,8] Severe hypoplasia of the pulmonary artery and the left ventricle may cause excessively high right ventricular pressure and heart failure following definitive repair. Since palliative procedures are available in this entity, indications for total correction have to be decided according to the method of correction and the surgical results in each institution. In order to determine the surgical indication based on a quantitative evaluation, several methods have been tried to quantify the size of the pulmonary artery, mainly in tetralogy of Fallot. These methods include the ratio of diameters of the pulmonic anulus against the aortic anulus[1] or the ratio of the mean diameter of the right and left pulmonary arteries against that of the descending aorta at the level of the diaphragm.[2] The diameter ratio of the main pulmonary trunk and the ascending aorta is influenced by the valvular and supravalvular stenosis and cannot be applied in patients with pulmonary atresia. The latter method is applicable in various diseases. However, standardization of values in different body sizes and different entities is a problem. Therefore, we utilized a cross-sectional area rather than the diameter to have a better correlation with the capacity of the pulmonary arteries and, for the sake of standardization, divided the resultant value by the body surface area.

The PA-index was found to be constant over a wide range of body surface areas from infancy to adolescence. Thus, the normal mean value of 330 ± 30 mm²/BSA can be applicable over a wide range of patients. In the measurement of the pulmonary artery in the control group, the mean value of the maximum and minimum diameters during a cardiac cycle was employed. Since the size of the pulmonary artery in cyanotic heart diseases with decreased blood flow showed almost no fluctuation owing to low intraluminal pressure in a cardiac cycle, the mean value in the control group should reflect a similar status rather than that seen in systole. Generally speaking, there was a difference of approximately 20% between PA-indexes during systole and diastole.[9-11] This was pointed out by Jarmakani and associates,[12] who reported on the size of the right pulmonary artery and demonstrated the pressure-radius relationship. Severe deformities of the pulmonary artery in the vicinity of the previous shunt occasionally cause difficulty in measuring diameter in cyanotic heart disease. The general principle of this PA-index is based on calculation of areas of the pulmonary arteries at their distal end where conventional angioplasty can be performed through a median sternotomy. Therefore, in case