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ORIGINAL ARTICLE

Effect of tranexamic acid on blood loss in pediatric cardiac surgery: a randomized trial

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Abstract
Purpose The benefit of tranexamic acid (TXA) in pediatric cardiac surgery on postoperative bleeding has varied among studies. It is also unclear whether the effects of TXA differ between cyanotic patients and acyanotic patients. The aim of this study was to test the benefit of TXA in pediatric cardiac surgery in a well-balanced study population of cyanotic and acyanotic patients.
Methods A total of 160 pediatric patients undergoing cardiac surgery with cardiopulmonary bypass (81 cyanotic, 79 acyanotic) were included in this single-blinded, randomized trial at a tertiary care university-affiliated teaching hospital. Eighty-one children (41 cyanotic, 40 acyanotic) were randomly assigned to a TXA group, in which they received 50 mg/kg of TXA as a bolus followed by 15 mg/kg/h infusion and another 50 mg/kg into the bypass circuit. The other 79 patients were randomly assigned to a placebo group. The primary end point was the amount of 24-h blood loss.
Results The amount of 24-h blood loss was significantly less in the TXA group than in the placebo group [mean (95% confidence interval): 18.6 (15.8–21.4) vs. 23.5 (19.4–27.5) ml/kg, respectively; mean difference −4.9 (−9.7 to −0.01) ml/kg; $p = 0.049$]. This effect of TXA was already significant at 6 h [9.5 (7.5–11.5) vs. 13.2 (10.6–15.9) ml/kg, respectively; mean difference −3.47 (−7.0 to −0.4) ml/kg; $p = 0.027$]. However, there was no significant difference in the amount of blood transfusion between the groups. There was also no statistical difference in the effect of TXA in each cyanotic and acyanotic subgroup.
Conclusion TXA can reduce blood loss in pediatric cardiac surgery but not the transfusion requirement (http://ClinicalTrials.gov number NCT00994994).

Keywords Tranexamic acid · Children · Cardiac surgery · Blood loss · Cyanosis

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Introduction

Excessive bleeding leads to increases in morbidity and mortality in adults [1] and children [2] after cardiac surgery with cardiopulmonary bypass (CPB). Excessive bleeding in children can be as large as 110 ml/kg/24 h [3], which necessitates blood transfusion, and allogeneic blood transfusion may increase mortality [4]. Although major causes of postoperative bleeding in pediatric cardiac surgery are thrombocytopenia, platelet dysfunction, and hemodilution, one possible cause is increased fibrinolysis during CPB [5, 6], which occurs in about 16% of patients [7]. Moreover, congenital heart disease itself in pediatric patients has been shown to be associated with fibrinolysis [8, 9].

Tranexamic acid (TXA), an analog of the amino acid lysine, is an antifibrinolytic agent that competes with

plasminogen for binding sites on fibrin and also prevents plasmin-induced platelet activation [10]. To date, there have been seven randomized control trials to assess the effect of TXA in pediatric cardiac surgery [11–17]. Four of those studies showed a significant reduction in postoperative blood loss by TXA [11, 12, 14, 16], whereas two studies showed no significant effect of TXA [15, 17], and one study showed mixed results depending on dose [13]. Although the presence of cyanosis would be associated with more bleeding episodes due to collateral vessel formation and platelet dysfunction caused by erythrocytosis [18], it is unclear whether there is a difference in the effects of TXA in cyanotic and acyanotic patients.

Accordingly, we conducted a randomized control study involving a well-balanced study population of cyanotic and acyanotic patients in order to determine the effect of TXA on blood loss in pediatric cardiac surgery patients.

Materials and methods

Our Institutional Review Board approved the study protocol. Written informed consent was obtained from the legal guardian of each patient because all participants were younger than 18 years of age.

Patient selection

Children younger than 18 years of age who were scheduled to undergo elective cardiac surgery with CPB between January 2006 and July 2007 were considered potentially eligible for inclusion in the study. Neonates of less than 1 month of age, children on mechanical ventilation preoperatively, and children on inotropic support before surgery were excluded from the study. Other exclusion criteria included a preexisting coagulation disorder, re-operation within 48 h, obvious kidney or liver disease, and known allergy to TXA. Preoperative anticoagulation therapy, such as administration of warfarin, aspirin, or ticlopidine, was considered acceptable for inclusion.

Group allocation

After informed consent had been obtained, participants were divided into a cyanotic congenital heart disease (CCHD) cohort and an acyanotic congenital heart disease (ACHD) cohort according to the presence of a right-to-left shunt region (oxygen saturation of <90%). The patients in each cohort were then randomly assigned to a TXA group or placebo group (1:1) in each cyanotic and acyanotic cohort. Randomization was stratified with the use of computer-based random-number generator lists provided by one of the co-investigators (HM) who was not involved in the determination of eligibility, administration of study drugs, patient's treatment, or assessment of outcomes.

Study protocol

In the TXA group, 50 mg/kg of intravenous TXA (100 mg/ml solution) was administered before skin incision; this was followed by 15 mg/kg/h of continuous infusion. Another 50 mg/kg of TXA was injected into a CPB circuit prior to commencement of the CPB. Continuous infusion was ceased with skin closure. Patients in the placebo group received an equivalent volume of normal saline, including continuous infusion and injection into the CPB circuit.

Perioperative management of patients

Management of general anesthesia was standardized. A blood sample was taken after the induction of anesthesia to check hemoglobin, platelet count, prothrombin time, and activated partial thromboplastin time (APTT).

Heparin (300 units/kg) was given for anticoagulation prior to aortic cannulation to maintain activated clotting time (ACT) (Hemochron 401 or 801; SOMA Technology, Bloomfield, CT) at more than 400 s. Priming volumes in CPB circuits were approximately 400, 600, 1200, and 1500 ml for patients with body weights of approximately <15, 15–25, 25–35, and >35 kg, respectively. The CPB circuit was primed with 25% albumin, mannnitol, sodium bicarbonate, and acetate Ringer's solution, with the ratio of amounts of acetate Ringer's fluid and albumin being maintained at approximately 5:1. Packed red blood cells were also added to the prime to achieve a hematocrit level of >25% if the body weight was <10 kg. Protamine at the dose of 3 mg/kg was injected after termination of CPB. If ACT was still more than 130 s, additional protamine was administered. If the surgeon considered that hemostasis was not achieved after protamine administration, fresh frozen plasma (FFP) was given to the patient. Although the anesthesiologists were responsible for intraoperative fluid management, including blood transfusion, platelet transfusion was performed after consultation with the responsible cardiac surgeon because of the cost issue. Our approximate targets for hemoglobin were 12 g/dl in patients with acyanotic status and 15 g/dl in patients with cyanotic status, although a clear-cut trigger of transfusion was not defined in this trial. We basically tried not to give any blood product to patients whose CPB circuit was filled without red cells. Left atrial pressure or central venous pressure was maintained at 5–10 mmHg to keep preload.

The patients were transferred to the intensive care unit (ICU) after confirming chest X-rays, and another blood sample was taken following the same protocol as used for the intraoperative collection. Postoperative management,

including blood product transfusion, was performed by attending physicians in the ICU, who were blinded to the study group. FFP was given if the physician considered that the patients required clotting factors based on the results of coagulation tests. Similarly, permission by the responsible surgeon was required for platelet transfusion while the patient was in the ICU.

Since this was a single-blinded randomized trial, anesthesiologists who cared for the participants were aware of the group allocation, but surgeons, intensive care physicians, operating and intensive care nurses, and perfusionists did not know the group assignment.

Outcomes

Our hypothesis was that TXA would reduce the amount of blood loss in pediatric cardiac surgery patients. The primary end point in this study was 24-h blood loss. Blood loss was defined as the total amount of pericardial and mediastinal tube drainage after admission to the ICU. The amount of drainage was noted in the medical chart recorded by ICU nurses who were not aware of group allocation. As secondary end points, 6-h blood loss, amount of transfusion required, chest closure time (from the time of protamine injection to skin closure), re-exploration of the chest for bleeding within 24 h, duration of mechanical ventilation, duration of ICU stay, and episodes of thrombotic complication were also recorded.

Power calculation

To calculate the sample size for the current trial, we considered a 50% reduction of blood loss during the first 24 h post-surgery to be satisfactory. Assuming an average blood loss of 35 ml/kg, a standard deviation of 25 ml/kg, a power of 0.80, and an alpha level of 0.05, 33 participants were required in each group. We increased the sample size to 40 to allow for loss to follow-up in each of the four groups. Therefore, the aim was to investigate 160 patients in the study.

Statistical analysis

Statistical analyses were performed by JMP ver. 7.0 (SAS Institute, Cary, NC). Data were expressed as the mean and 95% confidence interval (95% CI). Student's t test or Wilcoxon's test was used for statistical analysis where applicable. Fisher's exact test or the chi-square test was used for categorical data. A p value <0.05 was considered to be statistically significant.

Results

We studied 160 children undergoing cardiac surgery with CPB. Eighty-one patients (41 cyanotic and 40 acyanotic patients) were assigned to the TXA group and 79 patients (40 cyanotic and 39 acyanotic patients) were assigned to the placebo group. All patients received a full-predefined dose of TXA, and none of the patients were lost to follow-up. Thus, we included data for all 160 patients in our final analyses (Fig. 1). The mean age of the patients was 32.5 (range 1–170) months and mean body weight was 10.6 (range 3.2–50.6) kg. There were 54 infants (33.8%) younger than 12 months. Although 56 (35%) of the children received anticoagulants prior to surgery, there was no association between anticoagulant therapy and preoperative APTT or PT. The patients

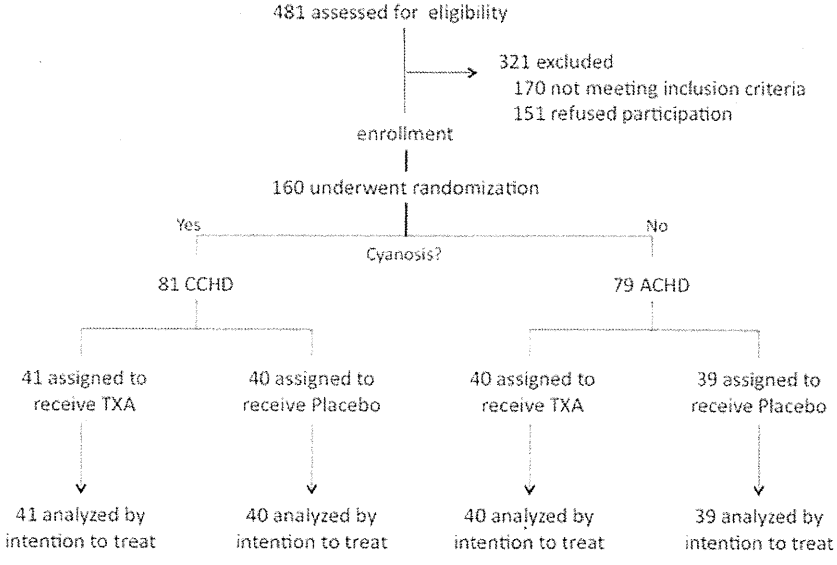

Fig. 1 Flow diagram of the study. None of the participants were lost to follow-up. *TXA* Tranexamic acid, *CCHD* cyanotic congenital heart disease, *ACHD* acyanotic congenital heart disease

received various types of operations, and 135 (84.4%) of the patients were in Risk Adjustment in Congenital Heart Surgery (RACHS-1) category [19] 2 or 3. Sixty-one (38.2%) of the patients had received previous sternotomy. The mean CPB time was 102.5 (95% CI 92.0–113.0) min and mean aortic cross clamp time was 64.5 (95% CI 59.2–69.9) min. All of these pre- and intra-operative variables were well balanced between the TXA and placebo groups, except number of patients whose APTT was above the normal limit (Table 1). There were 24 (29.6%) children in the TXA group compared with 41 (52.6%) children in the placebo group with supranormal APTT ($p = 0.004$).

Primary and secondary endpoints

The mean amount of drainage at 24 h post-surgery was 18.6 (95% CI 15.8–21.4) ml/kg in the TXA group and 23.5 (19.4–27.5) ml/kg in the placebo group; the difference between the groups was statistically significant [mean difference −4.9 (−9.7 to −0.01) ml/kg; $p = 0.049$]. This effect of TXA on the amount of bleeding was already significant at 6 h after the operation [9.5 (7.5–11.5) ml/kg in the TXA group vs. 13.2 (10.6–15.9) ml/kg in the placebo group; mean difference −3.7 (−7.0 to −0.4) ml/kg; $p = 0.027$] (Fig. 2).

Table 1 Characteristics of patients and surgery

Characteristics of patients/surgery	Total	TXA	Placebo	*p* value
Age (months)	32.5 (26.1–36.3)	31.2 (24.5–37.9)	31.3 (23.5–39.1)	0.99
Age in CCHD (months)		27.9 (22.6–33.2)	36.6 (25.0–48.0)	0.18
Infants (<12 month)	54	28 (34.6%)	26 (32.9%)	0.87
Gender (male)	84 (52.5%)	42 (51.9%)	42 (53.2%)	0.99
Height (cm)	80.9 (77.7–84.2)	81.8 (77.3–86.4)	80.0 (75.4–84.7)	0.58
Weight (kg)	10.6 (9.5–11.7)	10.9 (9.4–12.3)	10.3 (8.7–12.0)	0.63
Preoperative anticoagulation		28	29	0.87
Aspirin	23	14	9	
Warfarin	22	10	12	
Ticlopidine	18	7	11	
Repeat sternotomy	61 (38.1%)	25 (30.9%)	36 (45.6%)	0.10
Surgeon A/B/C	87/46/27	48/22/11	39/24/16	0.41
Preoperative laboratory data				
Hemoglobin (Hb) (g/dl)	12.8 (12.5–13.2)	12.9 (12.3–13.4)	12.8 (12.3–13.4)	0.86
Hb in CCHD (g/dl)		14.3 (13.6–15.0)	14.3 (13.6–15.0)	0.97
Platelets ($\times 10^3$/ml)	300 (284–315)	287 (266–309)	312 (291–334)	0.11
Prothrombin time (%)	94.2 (92.0–96.4)	93.5 (90.4–96.6)	94.9 (91.8–98.1)	0.53
APTT (s)	41.7 (36.8–46.5)	39.6 (32.8–46.4)	43.9 (36.9–50.7)	0.39
Creatinine (mg/dl)	0.29 (0.27–0.30)	0.29 (0.27–0.31)	0.28 (0.26–0.30)	0.77
Procedures				0.65
ASD/VSD closure	54 (33.8%)	27 (33.3%)	27 (34.2%)	1.0
TCPC	29 (18.1%)	15 (18.5%)	14 (17.7%)	1.0
TOF repair	23 (14.4%)	11 (13.6%)	12 (15.2%)	1.0
AVSD repair	10 (6.3%)	6 (7.4%)	4 (5.1%)	1.0
BDG	9 (5.6%)	4 (4.9%)	5 (6.3%)	0.74
Rastelli	7 (4.4%)	4 (4.9%)	3 (3.8%)	1.0
CPB time (min)	102.5 (92.0–113.0)	97.2 (87.0–107.4)	107.9 (89.2–126.7)	0.31
ACC time (min)	64.5 (59.2–69.9)	65.5 (58.5–72.6)	63.5 (55.4–71.7)	0.71
Temp during CPB (°C)	29.9 (29.3–30.4)	29.9 (29.1–30.7)	29.8 (29.1–30.6)	0.92
Blood prime	76 (47.5%)	40 (49.4%)	36 (45.6%)	0.64

Data are expressed as the mean with the 95% confidence interval (95% CI) in parentheses, or as the number of patients with the percentage in parentheses

TXA Tranexamic acid, *CCHD* cyanotic congenital heart disease, *APTT* activated partial thromboplastin time, *ASD* atrial septal defect, *VSD* ventricular septal defect, *TCPC* total cavo-pulmonary connection, *TOF* tetralogy of fallot, *AVSD* atrioventricular septal defect, *BDG* bidirectional Glenn, *CPB* cardiopulmonary bypass, *ACC* aortic cross clamp, *Temp* temperature

There were only two patients requiring re-exploration of the chest for bleeding in both groups. Transfusions of blood products were required by 59 (72.8%) of the patients in the TXA group and 66 (83.5%) of the patients in the placebo group ($p = 0.13$). There were no significant differences between the groups in terms of the amount of blood products administered during the operation and for 24 h post-surgery and of the number of patient donor exposures. Mechanical ventilation in the ICU was required by 58 (72.5%) of the patients in the TXA group and 63 (78.8%) of the patients in the placebo group, and there was no significant difference in the mean duration of mechanical ventilation between the groups. The mean duration of ICU stay was not different between the groups ($p = 0.32$), and chest closure time was also not different between the groups (Table 2). Only one patient in the TXA group suffered from cerebral infarction at approximately 2 weeks post-surgery. Although the cause of infarction was not proven, it was considered to be a thrombotic complication. However, the neurological status of this patient gradually improved on an outpatient clinic basis. Although TXA is eliminated by urinary excretion, there were no significant differences in pre- and postoperative creatinine values between the TXA and placebo groups (Tables 1, 2).

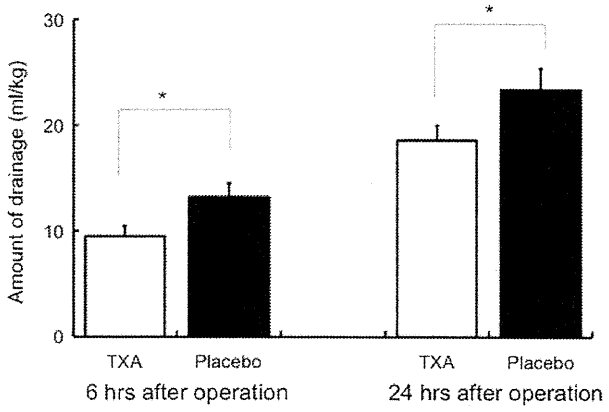

Fig. 2 Blood loss in patients assigned to the TXA and placebo groups at 6 and 24 h post-surgery. *White bar* TXA, *black bar* placebo. *Vertical line above bars* Standard error (SE). *$p < 0.05$

Subgroup analysis

Based on our protocol definition, we included 81 cyanotic and 79 acyanotic patients. The mean amount of 24-h drainage was significantly greater in the cyanotic patients than in the acyanotic patients [24.9 (21.3–28.6) vs. 17.0 (13.9–20.1) ml/kg, respectively; mean difference 7.9 (3.2–12.7) ml/kg; $p = 0.0012$]. There was no interaction between cyanotic status and TXA treatment ($p = 0.66$). There was a similar difference between the cyanotic and acyanotic patients in amount of drainage at 6 h post-surgery [13.0 (10.6–15.4) vs. 9.6 (7.3–11.9) ml/kg; mean difference 3.4 (0.1–6.7) ml/kg; $p = 0.045$]. Although there were trends for a benefit of TXA in both the cyanotic and acyanotic patients, there were no statistical differences in any subgroups (Fig. 3).

For the 61 children who underwent repeat sternotomy, there were also no significant differences in blood loss at 6

Table 2 Amounts of blood products administered during the operation and for 24 h after the operation and other outcomes

Use of blood products	TXA	Placebo	Mean difference (95% CI)	*p* value
Re-exploration of chest	2	2		0.99
Transfusion	59 (72.8%)	66 (83.5%)		0.13
PRBC (ml/kg)	54 (66.7%)	58 (73.4%)		0.35
OR	14.4 (10.2–18.5)	21.4 (13.4–29.3)	−7.0 (−15.6 to 1.6)	0.12
ICU	13.2 (10.5–15.9)	15.6 (11.8–19.4)	−2.4 (−7.0 to 2.2)	0.3
Total	21.9 (18.0–25.7)	26.3 (20.1–32.6)	−4.5 (−11.9 to 2.9)	0.23
FFP (ml/kg)	56 (69.1%)	61 (77.2%)		0.25
OR	13.3 (10.6–16.0)	15.2 (11.9–18.6)	−1.9 (−6.2 to 2.3)	0.36
ICU	13.8 (11.1–16.6)	13.2 (10.4–16.0)	0.6 (−3.3 to 4.5)	0.76
Total	24.9 (21.2–28.6)	26.3 (22.4–30.3)	−1.5 (−6.8 to 3.9)	0.59
PC (ml/kg)	24 (29.6%)	20 (25.3%)		0.54
OR	12.9 (9.6–16.1)	15.3 (10.4–20.3)	−2.5 (−7.9 to 3.0)	0.36
ICU	14.6 (8.4–20.8)	11.0 (4.3–17.8)	3.6 (−5.2 to 2.3)	0.41
Total	18.7 (14.6–22.9)	16.4 (11.8–20.9)	2.4 (−3.6 to 8.3)	0.43
Chest closure time (min)	58.3 (52.6–64.1)	58.8 (53.7–63.9)	−4.6 (−8.1 to 7.2)	0.90
MV in the ICU	58 (71.6%)	63 (79.7%)		0.37
Duration of MV (h)	35.9 (9.0–62.9)	66.9 (4.3–129.5)	−31.0 (−98.8 to 36.9)	0.37
ICU stay (days)	5.6 (3.9–7.2)	7.4 (4.1–10.7)	−1.8 (−5.5 to 1.8)	0.32
Postope creatinine (mg/dl)	0.30 (0.29–0.32)	0.30 (0.29–0.33)	0.30 (0.27 to 0.31)	0.34

Data are expressed as the mean with the 95% CI in parentheses, or as the number of patients with the percentage in parentheses

PRBC packed red blood cells, *OR* operating room, *ICU* intensive care unit, *FFP* fresh frozen plasma, *PC* apheresis platelet concentrate, *MV* mechanical ventilation

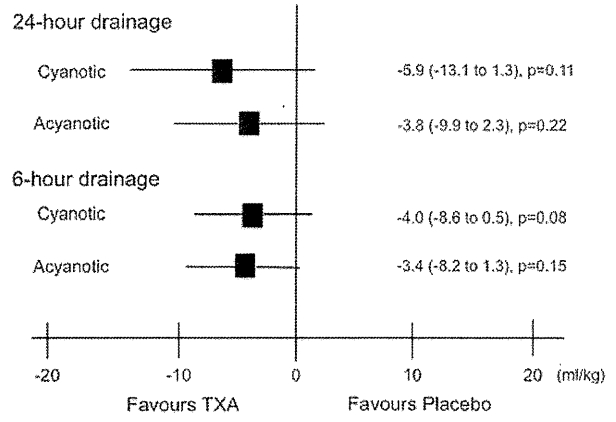

Fig. 3 Differences in blood loss with TXA and placebo. *X*-axis represents units in milliliters per kilogram. *Black squares* Mean, *bars* 95% confidence interval (95% CI). Data are given as the mean differences (95% CI)

and 24 h post-surgery between the TXA and placebo groups [20.0 (14.0–25.9) vs. 25.1 (19.9–30.2) ml/kg at 24 h, $p = 0.201$; 11.0 (7.2–14.7) vs. 13.0 (9.8–16.2) ml/kg at 6 h, $p = 0.404$]. There was also no significant difference in blood loss between patients with repeat sternotomy and those with non-repeat sternotomy [22.9 (19.0–26.9) vs. 19.8 (16.7–22.9) ml/kg/24 h, respectively, $p = 0.227$; 12.1 (9.4–14.8) vs 10.8 (8.7–13.0) ml/kg/6 h, respectively, $p = 0.454$].

Discussion

We conducted a randomized control trial to assess the benefit of TXA in pediatric cardiac surgery cohorts, in which cyanotic and acyanotic patients were well balanced (1:1 ratio). In this study, TXA significantly reduced blood loss, but it did not alter the amount of blood products administered.

Our study included a larger number of participants than the seven previously reported studies. It also included equal numbers of patients with CCHD and ACHD, which is in contrast to most of the previous studies in which the respective patient populations were not well balanced with respect to CCHD/ACHD. All previous studies were single-center studies as was our study. Of these seven earlier studies, two were double-blinded studies that showed negative effects of TXA on both bleeding and amount of transfusion products required [15, 17]. A recent study by Bulutcu et al. [11] that included 50 children and in which anesthesiologist and perfusionists were not blinded to patients allocation showed that TXA was effective in terms of both blood loss and transfusion. Three studies conducted by the same group showed desirable effects of TXA [12–14]. However, these studies appear to be non-blind studies and the method of randomization is unclear. Nevertheless, they included relatively large numbers of patients, while other studies had fewer than 100 participants. The proportion of cyanotic patients varied among these earlier studies. Three studies included both patients with CCHD and patients with ACHD [15–17]. However, two of these studies failed to show any benefit of TXA [15, 17]. On the other hand, four recent studies in which the participants were all cyanotic patients did show beneficial effects of TXA [11–14]. Since it is not clear whether the benefits of TXA in patients with CCHD differ from those in patients with ACHD, a randomized control trial including equal numbers of patients with and without cyanosis might be desirable. Our results of just such a trial in which relatively equal numbers of cyanotic and acyanotic patients were enrolled demonstrate that TXA has similar effects among these two patient populations.

There is a large variation (10–100 mg/kg) in the recommended dose in pediatric cardiac surgery [11–17]. A single bolus of 50 mg/kg showed no benefit on blood loss in three trials [13, 15, 17], but a larger dose of 100 mg/kg followed by continuous infusion or an additional dose of TXA did show effects [11, 16]. Dowd et al. [20] reported that plasma concentration rapidly fell after the initiation of CPB in adult patients and continued to fall over time despite infusion at 1 mg/kg/h. Thus, our protocol using continuous infusion following a bolus may be adequate to maintain the plasma concentration of TXA in pediatric patients. A possible risk of using a high dose of TXA is the occurrence of seizures seen in adult cardiac surgery [21, 22]. We had one case of cerebral infarction, but there were no other neurological complications. Thus, further investigation is needed to determine the appropriate doses of TXA in both adults and children.

The amount of blood transfusion was not significantly different in the TXA group and placebo group in our study. This is consistent with the results of another study showing that there was no significant difference in transfusion despite the fact that blood loss was significantly different [16]. On the other hand, the blood transfusion requirement was lower in cyanotic patients in the TXA treatment group in previous studies [11–14]. However, we did not find any statistical difference in the amount of blood transfusion between the TXA groups and the placebo groups in the CCHD cohort and ACHD cohort. However, the fact that we did not implement a detailed transfusion protocol in the current trial might be a confounding factor. Standard practice at our hospital is not to encourage blood transfusion when CPB circuits are primed without red cells. We also encountered the situation in which patients required

intravascular volumes even if there was no bleeding. Intraoperative transfusion practice was determined by individual anesthesiologists. Both of these practices can also be confounding factors. Moreover, the amount of blood loss could be affected by the amount of platelets and/or FFP given during and after surgery because these would promote the coagulation cascade [23]. However, the amount of such products was not different between the groups. Significant but only small differences in blood loss could be a reason why the amount of blood transfusion did not reach statistical significance.

Since bleeding leads to increased morbidity and mortality in children [2], our results show possible benefits of TXA. However, there are several limitations to our study. First, this was a single-center trial. Thus, our findings may not be applicable to other pediatric cardiac centers. Second, the assessment of results was not blinded and this can be a bias. Although anesthesiologists knew about group allocation, the decision to give blood products was made by many physicians. Thus, this effect might not be strong. Third, neonates of less than 1 month of age were excluded from this study because, compared to other age groups, coagulation disorders in this age group are known to be much stronger [24, 25], and the amount of blood loss in neonates has been shown to be much larger [7, 26]. Since TXA showed a minimal clinical effect on blood loss in our study population, whether it can benefit neonates or other patients at high risk for bleeding is unknown.

Prior sternotomy would be one of the risk factors for postoperative bleeding in this cohort. Although it did not reach statistical significance, the number of patients with repeat sternotomy was greater in the placebo group than in the TXA group in our study. However, the amount of blood loss was not different between repeat sternotomy patients and non-repeat sternotomy patients.

We allowed patients who were taking anticoagulant medicine prior to surgery to enroll in our study. In our basic strategy, patients are requested to cease all anticoagulants 7 days before surgery. Thus, APTT or PT after anesthetic induction was normalized in most patients. Although the number of children whose APTT was above normal was greater in the placebo group than in the TXA group, there was no difference in blood loss between patients with normal APTT and those with supranormal APTT. Thus, these effects could be negligible.

In conclusion, we have shown a small beneficial effect of TXA in reducing blood loss in pediatric cardiac surgery patients who are not at high risk for bleeding. There was no difference in the effects of TXA to reduce blood loss between cyanotic and acyanotic patients. Routine use of this medication for these patients should be entrusted to each institution.

References

1. Belisle S, Hardy JF. Hemorrhage and the use of blood products after adult cardiac operations: myths and realities. Ann Thorac Surg. 1996;62:1908–17.
2. Petaja J, Lundstrom U, Leijala M, Peltola K, Siimes MA. Bleeding and use of blood products after heart operations in infants. J Thorac Cardiovasc Surg. 1995;109:524–9.
3. Manno CS, Hedberg KW, Kim HC, Bunin GR, Nicolson S, Jobes D, Schwartz E, Norwood WI. Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. Blood. 1991;77:930–6.
4. Kneyber MC, Hersi MI, Twisk JW, Markhorst DG, Plotz FB. Red blood cell transfusion in critically ill children is independently associated with increased mortality. Intensive Care Med. 2007;33:1414–22.
5. Miller BE, Guzzetta NA, Tosone SR, Levy JH. Rapid evaluation of coagulopathies after cardiopulmonary bypass in children using modified thromboelastography. Anesth Analg. 2000;90:1324–30.
6. Eisses MJ, Chandler WL. Cardiopulmonary bypass parameters and hemostatic response to cardiopulmonary bypass in infants versus children. J Cardiothorac Vasc Anesth. 2008;22:53–9.
7. Williams GD, Bratton SL, Riley EC, Ramamoorthy C. Association between age and blood loss in children undergoing open heart operations. Ann Thorac Surg. 1998;66:870–5. (discussion 5–6).
8. Ekert H, Gilchrist GS, Stanton R, Hammond D. Hemostasis in cyanotic congenital heart disease. J Pediatr. 1970;76:221–30.
9. Williams GD, Bratton SL, Nielsen NJ, Ramamoorthy C. Fibrinolysis in pediatric patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 1998;12:633–8.
10. Eaton MP. Antifibrinolytic therapy in surgery for congenital heart disease. Anesth Analg. 2008;106:1087–100.
11. Bulutcu FS, Ozbek U, Polat B, Yalçin Y, Karaci AR, Bayindir O. Which may be effective to reduce blood loss after cardiac operations in cyanotic children: tranexamic acid, aprotinin or a combination? Paediatr Anaesth. 2005;15:41–6.
12. Chauhan S, Das SN, Bisoi A, Kale S, Kiran U. Comparison of epsilon aminocaproic acid and tranexamic acid in pediatric cardiac surgery. J Cardiothorac Vasc Anesth. 2004;18:141–3.
13. Chauhan S, Bisoi A, Kumar N, Mittal D, Kale S, Kiran U, Venugopal P. Dose comparison of tranexamic acid in pediatric cardiac surgery. Asian Cardiovasc Thorac Ann. 2004;12:121–4.
14. Chauhan S, Bisoi A, Modi R, Gharde P, Rajesh MR. Tranexamic acid in paediatric cardiac surgery. Indian J Med Res. 2003;118:86–9.
15. Levin E, Wu J, Devine DV, Alexander J, Reichart C, Sett S, Seear M. Hemostatic parameters and platelet activation marker expression in cyanotic and acyanotic pediatric patients undergoing cardiac surgery in the presence of tranexamic acid. Thromb Haemost. 2000;83:54–9.
16. Reid RW, Zimmerman AA, Laussen PC, Mayer JE, Gorlin JB, Burrows FA. The efficacy of tranexamic acid versus placebo in decreasing blood loss in pediatric patients undergoing repeat cardiac surgery. Anesth Analg. 1997;84:990–6.
17. Zonis Z, Seear M, Reichert C, Sett S, Allen C. The effect of preoperative tranexamic acid on blood loss after cardiac operations in children. J Thorac Cardiovasc Surg. 1996;111:982–7.
18. Mauer HM, McCue CM, Caul J, Still WJ. Impairment in platelet aggregation in congenital heart disease. Blood. 1972;40:207–16.
19. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg. 2002;123:110–8.

20. Dowd NP, Karski JM, Cheng DC, Carroll JA, Lin Y, James RL, Butterworth J. Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. Anesthesiology. 2002;97:390–9.
21. Martin K, Wiesner G, Breuer T, Lange R, Tassani P. The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients. Anesth Analg. 2008;107: 1783–90.
22. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg. 2010;110: 350–3.
23. Miller BE, Mochizuki T, Levy JH, Bailey JM, Tosone SR, Tam VK, Kanter KR. Predicting and treating coagulopathies after cardiopulmonary bypass in children. Anesth Analg. 1997;85: 1196–202.
24. Kern FH, Morana NJ, Sears JJ, Hickey PR. Coagulation defects in neonates during cardiopulmonary bypass. Ann Thorac Surg. 1992;54:541–6.
25. Petaja J, Peltola K, Sairanen H, Leijala M, Kekomaki R, Vahtera E, Siimes MA. Fibrinolysis, antithrombin III, and protein C in neonates during cardiac operations. J Thorac Cardiovasc Surg. 1996;112:665–71.
26. Williams GD, Bratton SL, Ramamoorthy C. Factors associated with blood loss and blood product transfusions: a multivariate analysis in children after open-heart surgery. Anesth Analg. 1999;89:57–64.

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ORIGINAL ARTICLE

Impact of chronic cyanosis and reoxygenation on the microheterogeneity of the myocardial blood flow: digital radiographic study in neonatal rats

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Abstract
Purpose. This study sought to show the heterogeneity of myocardial blood flow in the chronically hypoxic infantile myocardium and its response to reoxygenation using a novel type of digital radiography.
Methods. Newborn rats were housed in a hypoxic chamber or in a normal chamber (controls). After 4 or 8 weeks, the control rats were ventilated with normoxic conditions, and the rats housed under hypoxia were ventilated with either hypoxic (cyanotic group) or normoxic conditions (reoxygenation group). Desmethylimipramine labeled with tritium (HDMI) was injected into the left ventricle, and both ventricular free walls were sectioned and sliced from the subepicardium to the subendocardium at 10 mm thickness. The within-layer distribution of HDMI density was measured by digital radiography, and its spatial heterogeneity (i.e., flow heterogeneity) was quantified by the coefficient of variation (CV) of flows.
Results. There were no differences in the CV between the groups in either ventricle at 4 weeks of age and no differences in the right ventricle at 8 weeks of age. There was a trend toward a higher left ventricular CV in the cyanotic group than in the control group at 8 weeks of age (0.637 ± 0.099 vs. 0.510 ± 0.060, $P = 0.06$). At 8 weeks of age, the CV was lower in both ventricles in the reoxygenation group than in those of the control and cyanotic groups.
Conclusion. The chronically hypoxic infantile myocardium exhibits regional flow heterogeneity similar to that observed in the normal myocardium in both ventricles and exhibits reduced flow heterogeneity in response to reoxygenation.

Key words Cyanotic heart · Microheterogeneity · Digital radiography · Myocardial blood flow

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Introduction

Regional myocardial blood flow shows considerable spatial heterogeneity (region-to-region flow variability) even in the normal state.[1,2] Here, "region-to-region flow variability"

means the difference between flows in small regions within myocardial layers (i.e., flow heterogeneity at the lowest level). Myocardial spatial flow heterogeneity is stable,[3] and its physiological significance is linked with the efficiency of the O_2 supply in the tissue. The determinants of the heterogeneity of regional myocardial flow are coronary vascular tone, coronary anatomy, and cardiac mechanical effects on coronary flow, in which vascular tone is essential.[4] Even at rest in the normal heart, the spatial flow heterogeneity is under the strong influence of vascular tone so regional O_2 supplies match well with myocardial O_2 requirements in those corresponding regions.

Owing to inherently high O_2 extraction in the myocardium, flow heterogeneity is highly sensitive to insufficient O_2 supply. That is, compensatory vasodilation in response to reduced O_2 supply increases regional flow and, accordingly, changes the spatial flow heterogeneity. Regional myocardial flow may be regulated to be less heterogeneous under acute hypoxia. Matsumoto et al. showed hypoxia-induced reduction of within-layer flow heterogeneity in rabbit hearts by digital radiography with 100-μm pixel resolution.[5] Focusing on the differences in regional myocardial O_2 extraction,[6] the same authors speculated that flow in originally low-flow regions increase to a higher degree under hypoxia because of relatively higher O_2 extraction in those low-flow regions. On the other hand, Austin et al. reported that regional myocardial flow is more heterogeneous under asphyxia or the maximally vasodilatory condition induced by adenosine administration than under normoxia, although the tissue size resolved (several hundred millimeters) is much larger than 100 μm.[4,7] The mechanism underlying the O_2 dependence of myocardial flow heterogeneity remains to be clarified.

Myocardium in infants with cyanotic congenital heart disease is exposed to chronic hypoxia, resulting from severe pulmonary stenosis or atresia, or a right-to-left shunt. A chronically hypoxic myocardium in patients with tetralogy of Fallot has depressed adenosine triphosphate (ATP), defects in oxidative metabolism, and subsequent depressed postoperative ventricular function.[8] In contrast, a substantial body of evidence shows that the chronically hypoxic myocardium is preconditioned to ischemic events, thereby protecting against severe ischemic insult.[9] These studies suggest that the physiological response of the chronically hypoxic myocardium to ischemia or reperfusion (reoxygenation) is different from that of the normal myocardium. The following hypotheses were examined in this study: (1) chronically hypoxic myocardium differs (in terms of vascular tone or local vascular regulation) from the normal myocardium, thereby differing from the normal myocardium in terms of myocardial flow heterogeneity; (2) the coronary vasoresponse to reoxygenation of chronically hypoxic myocardium differs from that of normal myocardium, thereby affecting the flow heterogeneity under reoxygenation of the chronically hypoxic myocardium differently from that of normal myocardium.

Digital radiography combined with the technique of tritium-labeled desmethylimipramine (HDMI), an α-adrenergic antagonist, deposition for assessing regional myocardial flow was used to test these hypotheses. This technique enables the assessment of myocardial flow distribution with a resolution of 100 mm, which is ideal for evaluating myocardial flow at a precapillary level.[5] The chronic hypoxic model was developed by housing neonatal rats under a hypoxic environment for 4 and 8 weeks, thereby mimicking tetralogy of Fallot or other cyanotic congenital heart disease undergoing intracardiac repair and reoxygenation as in humans during infancy or childhood.[10]

Materials and methods

The experimental protocol was approved by the Committee on Animal Research at Okayama University, Japan. The animals were treated in compliance with the Principles of Laboratory Animal Care established by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals established by the Institute of Laboratory Animal Resources and published by the National Institute of Health (NIH publication 86-23, revised 1985).

Animal preparation

Sprague-Dawley pregnant female rats were housed in ambient air. Within 24 h after delivery, the neonatal rats and their mother rat were moved into a hypoxic chamber (cyanotic group) or a normal cage under ambient air (controls) and housed together during the lactation period. Thereafter, the neonatal rats were housed alone until the age of 4 or 8 weeks. O_2 and CO_2 concentrations in the hypoxic chamber were maintained at 12%–14% and <0.4%, respectively, using a custom-made hypo-O_2 producing device (Teijin, Tokyo, Japan). The gas concentrations were continuously monitored using a gas analyzer (ML206; AD Instruments, Sydney, Australia) and recorded by commercially available software (PowerLab; AD Instruments). Humidity was maintained at <75% and the temperature at 23°–27°C. These concentrations were monitored with a hygrothermometer (TRH-7X; Shinyei, Kobe, Japan). The animals were kept under a 12:12-h light–dark cycle; and standard rat chow and tap water were provided ad libitum.

Digital radiographic study

Preparation and ventilation

After 4 or 8 weeks of chronic hypoxia, animals were placed in the ambient environment and anesthetized with pentobarbital sodium (30 mg/kg i.p.). Body temperature was maintained at 37°–38°C on a heating blanket. After endotracheal intubation through a tracheotomy, each animal was artificially ventilated with a tidal volume of 10 ml/kg and a frequency of 55–65 strokes/min. The rats in the Control group ($n = 6$ and 7 at the ages of 4 and 8 weeks, respectively) were ventilated normally with a fraction of inspired O_2 (FiO_2) of 0.34–0.38. Electrocardiograms were continuously recorded on a direct-writing system (model RM6200; Nihon Kohden, Tokyo, Japan). A femoral vein was cannulated for drug infusion and blood sampling. A carotid or femoral artery was cannulated for arterial blood gas measurement. The heart was exposed by a median sternotomy. Arterial partial pressures of O_2 (PO_2) and CO_2 (PCO_2) and the pH were adjusted to be within physiological limits. The rats in the Cyanotic group ($n = 6$ each at the ages of 4 and 8 weeks) were ventilated with a "hypoxic" setting where FiO_2 and CO_2 fractions were 0.12–0.14 and <0.01, respectively. In the third group (reoxygenation group), the cyanotic animals ($n = 6$ each at the ages of 4 and 8 weeks, respectively) were subjected to "normal" ventilation in the same manner as in the control group.

Sample preparation

After the hemodynamics were stabilized and the ventilatory setting was adjusted based on the blood gas analysis, 20 μCi of desmethylimipramine labeled with tritium (HDMI), molecular weight 302.8 (no. NET 593; Du Pont-New England Nuclear, Waltham, MA, USA) was injected into the left ventricle (LV) through the apex using a 0.1-ml glass syringe over a period of 4–5 s. One minute after the injection of HDMI, the heart was arrested with an intravenous injection of a saturated potassium chloride solution and harvested en bloc. In the reoxygenation group, it took about 40 min from the start of reoxygenation to harvest. After the blood was washed out by saline, the free walls of the LV and the right ventricle (RV) were excised. The samples were sandwiched in aluminum sheets without compression and immediately placed in a −80°C freezer. The frozen sample was then sliced into more than 20 slices at 10 μm thickness from the subepicardium to the subendocardium by a cryostat microtome (HM505EVA; Zeiss, Hennigsdorf, Germany). Each slice was then placed on a slide glass and dried overnight.

Digital radiographic analysis

The digital radiographic technique is described in detail elsewhere.[5,11] Briefly, the slices were exposed to an imaging plate (IP-TR2040; Fujix, Kyoto, Japan), a two-dimensional sensor of tritium-sensitive radioactive energy, for 3 days in a lead-shielded box. The distribution of regional tissue radioactivity recorded on the imaging plate was converted to 16-bit digital data with 100-μm pixels by Bio-imaging analyzer (model HGE; Fujix), and the relative flow distribution was visualized with a 66536-step gradation. The mean background density was <5% of that of a region overlying the tissue.

For the analysis of within-layer flow distribution, 6–10 digital radiograms were arbitrarily selected from the subepicardium and the subendocardium of LV and RV free walls. Epicardial layer images showing a large coronary vessel trace were excluded from the study. Corrected for background activity, the heterogeneity of within-layer flows was quantitated by calculating the coefficient of pixel-to-pixel flow variation (CV; standard deviation/mean) in a square portion (3 × 3 mm to 6 × 6 mm) of each image. Figure 1 shows typical examples of within-layer flow distribution in the LV for three groups. The shading of the images is proportional to regional flow.

Morphometric and hemodynamic measurements

The body weight; weights of the whole heart (WH), RV, and LV; the thicknesses of the RV and LV free walls, and the hematocrit were measured. In another set of 8-week-old cyanotic ($n = 10$) and normal ($n = 7$) rats, the arterial blood pressure and heart rate were measured before and after sternotomy. The changes in the blood pressure and heart rate from hypoxic to normal ventilation were also recorded in the cyanotic rats. The blood pressure was measured using a pressure transducer (model 420-4; Camino Labs) and a manometer catheter (model 110-4 Fr; Camino Labs, San Diego, CA, USA) that had been inserted into the internal carotid artery.

Statistical methods

The data are presented as the mean ± SD. The level of statistical significance was set at $P < 0.05$. Differences among the three groups were analyzed by an analysis of variance (ANOVA) followed by post-hoc tests. Differences between groups were assessed by F-test followed by an unpaired *t*-test or the Mann-Whitney U-test. The CV was assessed by the Mann-Whitney U-test.

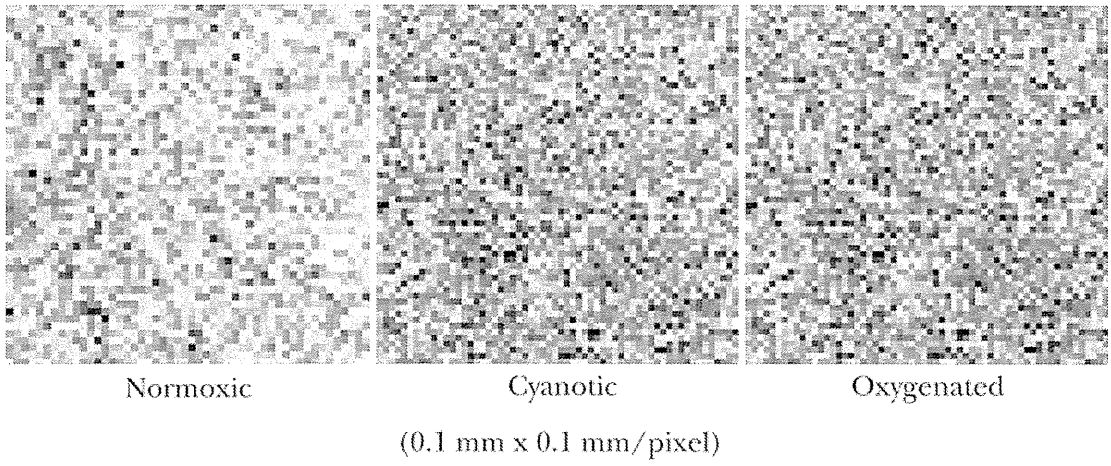

Fig. 1 Typical examples of desmethylimipramine labeled with tritium (HDMI) tracer images showing within-layer flow distributions in the left ventricular (LV) myocardium in control, cyanotic, and reoxygenated heart tissue

Table 1 Body and heart weights and ventricular wall thickness in normal and cyanotic myocardium

Parameter	4 Weeks			8 Weeks		
	Cyanotic ($n = 15$)	Control ($n = 7$)	P	Cyanotic ($n = 12$)	Control ($n = 8$)	P
Body weight (g)	75 ± 25	138 ± 30	<0.0001	166 ± 33	324 ± 17	<0.0001
Whole heart (g)	0.48 ± 0.16	0.66 ± 0.15	<0.05	0.84 ± 0.21	1.08 ± 0.12	<0.05
WH/BW × 10^{-2}	0.66 ± 0.19	0.49 ± 0.11	<0.05	0.50 ± 0.12	0.34 ± 0.04	<0.01
LV weight (g)	0.27 ± 0.11	0.37 ± 0.13	0.07	0.47 ± 0.14	0.60 ± 0.13	<0.05
LV weight/WH	0.56 ± 0.12	0.56 ± 0.14	0.97	0.55 ± 0.07	0.56 ± 0.11	0.95
RV weight (g)	0.12 ± 0.06	0.10 ± 0.04	0.38	0.18 ± 0.06	0.18 ± 0.06	0.96
RV weight/WH	0.25 ± 0.07	0.15 ± 0.07	<0.05	0.22 ± 0.04	0.17 ± 0.04	<0.05
RV/LV ratio	0.45 ± 0.13	0.27 ± 0.10	<0.01	0.40 ± 0.11	0.31 ± 0.12	0.10
Hematocrit (%)	46 ± 6	43 ± 3	0.21	56 ± 7	45 ± 5	<0.001
LV thickness (mm)	2.61 ± 0.54	2.57 ± 0.60	0.90	2.65 ± 1.15	4.21 ± 1.32	<0.05
RV thickness (mm)	1.66 ± 0.46	1.49 ± 0.58	0.48	2.52 ± 0.96	1.38 ± 0.18	<0.05

WH, whole heart; BW, body weight; LV, left ventricle; RV, right ventricle

Results

Characteristics of the cyanotic rat model

The body weights were significantly lower in the 4- and 8-week-old cyanotic rats in comparison to those in age-matched control rats ($P < 0.0001$) (Table 1). Cyanotic rat hearts show RV hypertrophy characterized by a higher WH-to-body weight ratio (WH/BW) and higher RV/WH ratio at both ages, and a higher RV/LV ratio at 4 weeks of age, in comparison to those in the age-matched control rats ($P < 0.05$ for all), although there was no difference in RV weight between the age-matched groups (Table 1). A higher hematocrit was found in the 8-week-old cyanotic rats than in the age-matched control rats ($P < 0.001$). The LV and RV wall thicknesses did not differ between the groups at 4 weeks of age. Smaller LV wall thickness and larger RV wall thickness were found in the 8-week-old cyanotic rats in comparison to those in the age-matched control rats ($P < 0.05$ for both).

Cyanotic versus control rats

Blood gases and hemodynamics are shown in Table 2. Arterial PaO_2 and saturation (SaO_2) were significantly lower in the cyanotic group than those in the control group. Cyanotic rats at 4 weeks of age were acidotic, characterized by lower pH and bicarbonate, in comparison to those in the age-matched control rats ($P < 0.01$). There was no difference in heart rate between the groups at either age. At 8 weeks of age, no sternotomy-induced change was found in the blood pressure or heart rate in both groups.

Table 2 Hemodynamic and metabolic parameters in normal, hypoxic, and reoxygenated myocardium

Parameter	4 Weeks				8 Weeks			
	Cyanotic ($n = 8$)	Oxygenated ($n = 7$)	Normal ($n = 7$)	P	Cyanotic ($n = 6$)	Oxygenated ($n = 6$)	Normal ($n = 8$)	P
HR (bpm)	349 ± 90	372 ± 28	421 ± 83	0.19	412 ± 76	383 ± 56	366 ± 23	0.30
pH	7.23 ± 0.09*	7.32 ± 0.04*	7.42 ± 006	<0.001	7.36 ± 0.04	7.43 ± 0.03	7.41 ± 0.05	<0.05
PaO_2 (mmHg)	50 ± 9*	162 ± 33	174 ± 39	<0.0001	43 ± 7*	192 ± 18	191 ± 39	<0.0001
$PaCO_2$ (mmHg)	33 ± 6	39 ± 9	35 ± 7	0.24	40 ± 3	37 ± 3	39 ± 5	0.46
HCO_3 (mmol/l)	14 ± 4*	20 ± 4	22 ± 4	<0.01	23 ± 1	25 ± 2	24 ± 2	0.31
SaO_2 (%)	77 ± 5*	99 ± 1	99 ± 1	<0.0001	76 ± 7*	100 ± 0	100 ± 1	<0.0001

HR, heart rate; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; HCO_3, bicarbonate; SaO_2, arterial saturation
*$P < 0.05$ in comparison to the normal group

Table 3 Myocardial blood flow heterogeneity of the left and right ventricle in normal, hypoxic, and reoxygenated myocardium

Parameter	4 Weeks			8 Weeks		
	Cyanotic ($n = 6$)	Oxygenated ($n = 6$)	Normal ($n = 6$)	Cyanotic ($n = 6$)	Oxygenated ($n = 6$)	Normal ($n = 7$)
LV	0.529 ± 0.170	0.393 ± 0.072	0.520 ± 0.148	0.637 ± 0.099	0.477 ± 0.118	0.510 ± 0.060
P	0.08	—	0.08	0.03	—	0.25
RV	0.581 ± 0.175	0.446 ± 0.063	0.547 ± 0.163	0.631 ± 0.136	0.467 ± 0.056	0.575 ± 0.086
P	0.15	—	0.26	0.03	—	0.02

P values are versus the reoxygenation group

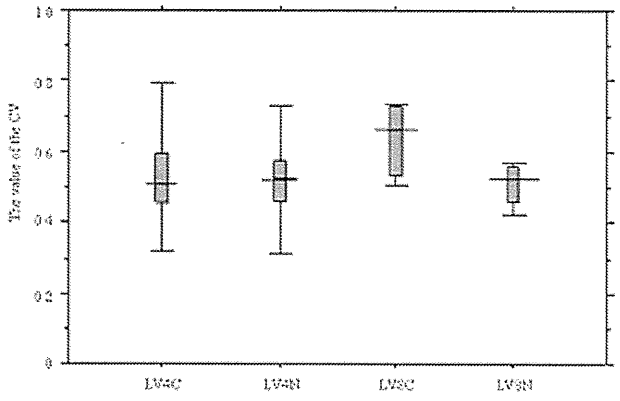

Fig. 2 Coefficients of variation (CV) of LV myocardial flow distribution in the cyanotic and control groups at 4 and 8 weeks of age. *Vertical bars* represent the standard deviations; *horizontal bars* across the boxes represent the median values. There was a trend toward a higher CV in the 8-week-old cyanotic rats than in age-matched control rats ($P = 0.06$)

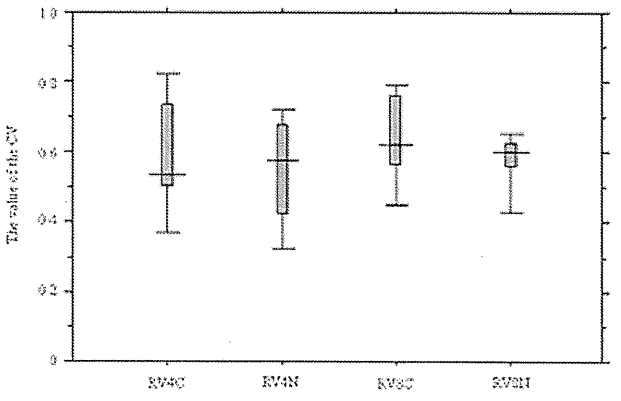

Fig. 3 Coefficients of variation (CV) of right ventricular (RV) myocardial flow distribution in the cyanotic and control groups at 4 and 8 weeks of age. *Vertical bars* represent the standard deviations; *horizontal bars* across boxes represent the median values

There was no significant difference in the CV of the LV myocardium (LVCV) between the cyanotic and control groups at 4 weeks of age (0.529 ± 0.170 vs. 0.520 ± 0.148) (Table 3; Fig. 2). There was a trend toward a higher LVCV in the cyanotic group than in the control group at 8 weeks (0.637 ± 0.099 vs. 0.510 ± 0.060, $P = 0.06$). No significant difference was found in the CV of the RV myocardium (RVCV) between the cyanotic and control groups at both 4 weeks of age (0.581 ± 0.175 vs. 0.547 ± 0.163, $P = 0.52$) and 8 weeks of age (0.631 ± 0.136 vs. 0.575 ± 0.086, $P = 0.48$) (Table 3; Fig. 3).

Age-related changes

The BW as well as the WH, LV, and RV weights increased with age in both groups (Table 1). The

hematocrit increased with age in the cyanotic group ($P < 0.01$) but not in the control group. The RV/LV ratio remained unchanged with age. The RV and LV wall thicknesses, respectively, increased with age in both the cyanotic and control groups (each $P < 0.05$). The heart rates remained unchanged with age in both groups. A significant degree of acidosis was found in the 4-week-old but not in the 8-week-old cyanotic rats.

Age-related changes in flow heterogeneity in the cyanotic and control groups are shown in Table 3. No significant age-dependent trend was found, although the CV tended to increase in LV myocardium in the cyanotic group ($P = 0.2$). In addition, no difference was observed in the CV of either the RV or LV myocardium between the 4- and 8-week-old control rats.

Effect of reoxygenation

The reoxygenation group (normally ventilated cyanotic rats) showed arterial PaO_2 and SaO_2 values that were similar to those observed in the control group (Table 2). Blood pressure tended to decrease after induction of normoxic ventilation (103 ± 18 vs. 88 ± 22 mmHg, $P = 0.14$); and the heart rate was not changed by the ventilatory setting (353 ± 39 vs. 360 ± 28 beats/min, $P = 0.68$).

When the cyanotic myocardium was reoxygenated, the CV became markedly smaller than in that in either ventricle in the cyanotic and control groups at 8 weeks of age (Table 3), although the difference was not statistically significant at 4 weeks of age. The CV of the 8-week LV in the reoxygenation group tended to be lower than that in the control group.

Left versus right ventricles

No difference was found in CV between the LV and RV myocardium although there was a trend toward a higher CV in RV myocardium than in LV myocardium in the 4-week-old reoxygenated and 8-week-old control groups (Table 3).

Discussion

When the heart is exposed to acute hypoxia, regional myocardial flow may become less heterogeneous as a response to an altered O_2 demand/supply balance,[5] thus leading to the hypothesis that local vascular control functions to improve the efficiency of regional O_2 delivery under hypoxia as a self-protective mechanism. The question raised in this study is whether the neonatal/infantile myocardium that is exposed to chronic hypoxia shows a similar level of flow heterogeneity observed under acute hypoxia and how the flow heterogeneity changes when exposed to a normoxic environment. The interest stems from the facts that patients with many types of congenital heart disease have cyanosis from birth because of pulmonary stenosis/atresia or an intracardiac mixing and that once intracardiac repair is performed the myocardium is suddenly exposed to a normoxic condition. This is the first study to investigate regional myocardial flow heterogeneity in a neonatal animal model mimicking the clinical sequence of cyanotic congenital heart diseases.

The new findings are that (1) myocardial blood flow heterogeneity in 4-week hypoxic hearts did not differ from that observed in age-matched control hearts in either the LV or the RV despite having significant somatic growth retardation and homeostatic changes (i.e., high hemoglobin, metabolic acidosis, RV hypertrophy). (2) Eight weeks of chronic hypoxia slightly increased the heterogeneity of regional myocardial flows in both the LV and RV. This tendency was noticeable in LV myocardium although no age-related changes were observed in myocardial blood flow heterogeneity. (3) Reoxygenation resulted in decreased flow heterogeneity in both the LV and RV in the 8-week hypoxic hearts.

Effect of chronic hypoxia on myocardial blood flow heterogeneity

The speculation was that myocardial blood flow could be less heterogeneous under chronic hypoxia than under normoxia. This was based on the fact that acute hypoxia leads to a decrease in regional myocardial flow heterogeneity. However, regional myocardial flow in chronically hypoxic myocardium was either similar to or highly heterogeneous in comparison to that of control normoxic myocardium. Even a slight increase in flow heterogeneity was observed in the 8-week cyanotic rats.

We speculated that this discrepancy between the present chronic and acute hypoxic models would result partly from their differences of vascular regulatory capacity. In the present study, we used the immature young rat raised in a hypoxic chamber from birth, whereas Matsumoto et al. used the mature adult rabbit raised normally.[5] In the heart under acute hypoxia, vascular regulation plays a contributing role in reducing flow heterogeneity probably through local coordination of vascular tone.[5] Such locally coordinated vasoregulation might not function under chronic exposure to hypoxia. Furthermore, coronary vascular anatomy and basal oxidative metabolism under chronic hypoxia, which differs from those in the normal heart,[12,13] may influence flow heterogeneity. That is, it is possible that these determining factors of flow heterogeneity were

modified under chronic exposure to hypoxia and resulted in similar or higher flow heterogeneity compared with that in the normoxic heart. Further studies are necessary for a better understanding of the influences of chronic hypoxia on these determinant factors of myocardial flow heterogeneity.

Erythrocytosis accompanying chronic hypoxia may also have an increasing effect on flow heterogeneity. Increased blood viscosity and hematocrit associated with erythrocytosis increase red blood cell (RBC) aggregation and the frequency of small vessel occlusion.[14–16] RBC aggregation occurs with higher frequency in low-flow regions and increases the frequency of the momentary blocking of microvessels preferably in low-flow regions,[17,18] thereby increasing flow heterogeneity.

Effect of reoxygenation on myocardial blood flow heterogeneity

The vasoresponse to reoxygenation is responsible for the decreased myocardial flow heterogeneity. Daniell and Bagwell showed that a sudden increase in FiO_2 (from 0.25 to 1.0) resulted in coronary flow decrease with decreased isometric systolic tension in open-chest dogs,[19] implying that the FiO_2 increase induced coronary vasoconstriction. The slight drop in blood pressure observed in this study when the ventilator setting changed indicates that reoxygenation may induce coronary constriction even in the heart exposed to chronic hypoxia.

The effect of reoxygenation or coronary constriction on flow heterogeneity, however, would be dependent on the degree of coronary tone under hypoxia. In the heart exposed to acute hypoxia, flow heterogeneity decreased, presumably owing to local vasoregulation.[5] However, regional myocardial flow shows a higher level of heterogeneity under more severe O_2 deprivation (anoxia) than under normoxia.[4,7] That is, the response of myocardial flow heterogeneity to acute hypoxia is biphasic according to the degree of O_2 supply deficiency. During the phase of reduced flow heterogeneity under acute hypoxia, the vascular tone is locally coordinated.[5] On the other hand, during the phase of increased flow heterogeneity, coronary vessels may be close to the maximum dilated condition because the flow heterogeneity under anoxia is similar to that in the heart at the adenosine-induced maximum vasodilatory state. Considering that reoxygenation decreased the myocardial flow heterogeneity in the chronically hypoxic heart, we speculated that its coronary vessels before reoxygenation might be near-maximum vasodilation, as in the anoxic heart, where locally coordinated vasoregulatory function does not work well. Thus, the decreased flow heterogeneity due to reoxygenation might be through the recovery of local coordination of coronary tone. As adenosine is a putative major vasoregulatory metabolite and has a preferential effect on small coronary arterioles,[20] reoxygenation might induce the constriction of small arterioles preferentially. Then the resultant decrease of coronary flow would also induce the constriction of larger resistance vessels via flow-dependent vascular responses. Elucidating the detailed mechanism underlying reoxygenation-induced vasoresponse under chronic hypoxia is, however, beyond the scope of this study.

Implications of the data

It is difficult to describe the clinical implications of the present results. Myocardial flow heterogeneity under 8-week chronic hypoxia looks similar to the normal state despite having significant physiological and somatic changes. In another words, the integrity of the myocardial microcirculation is not compromised with chronic hypoxia, at least in resting conditions. This finding is correlated with other studies looking at the metabolism of chronically hypoxic myocardium.[21,22] Silverman et al. showed that myocardial ATP and creatine phosphate levels are maintained at rest, but they are severely depleted at cardioplegic cardiac arrest in a chronically cyanotic canine model.[21] Assessments of flow heterogeneity in hypoxic myocardium under the condition of the maximum stress, such as cardioplegic cardiac arrest or β-receptor stimulation, may be helpful for determining whether myocardial flow heterogeneity under chronic hypoxia, including its response to reoxygenation, is protective or detrimental to myocardium.

Validation of the animal model

A rat exposed to chronic hypoxia has been established as an animal model for testing various medical and surgical interventions for cyanotic congenital heart diseases.[23,24] It has also been used as a model for primary pulmonary hypertension.[10] Chronic hypoxia induces suprasystemic RV systolic pressure as a result of high pulmonary vascular resistance and subsequent significant RV hypertrophy. The hemodynamics and physiology of this model is close to those in the moderate to severe form of tetralogy of Fallot accompanying high RV pressure and RV hypertrophy due to significant RV outflow tract obstruction. The mean PaO_2 of 50 mmHg and SaO_2 of 77% observed in the present hypoxic model are close to the values in patients undergoing elective repair for tetralogy of Fallot at 5–6 months of age.[25] This model, however, does not resemble the intracardiac mixing-type cyanotic congenital heart diseases that are usually exposed to some degree of volume overload, not

a significant pressure overload and hence no or minimal ventricular hypertrophy. In summary, this chronic model reproduces the clinical physiology of tetralogy of Fallot and its variant quite adequately, and therefore it is considered to be a reasonable animal model to investigate the collective effect of chronic cyanosis and pressure overload on myocardial blood flow heterogeneity.

Digital radiography

Digital radiography using a molecular flow tracer is a useful method for visualizing regional myocardial flow distribution at microvascular levels. The microsphere method has been a gold standard technique to measure regional myocardial flow; however, embolization of the microsphere itself and flow biasing at vascular bifurcations makes it difficult to measure regional flow at the microvascular level.[1] Tritium-labeled DMI is an ideal molecular flow tracer; it is delivered to tissue in proportion to the local flow, nearly completely extracted during a single pass, and stably deposited at α_2-receptors almost exclusively in capillaries. Furthermore, the path length of a b-particle emitted from tritium is short (on average 1.1 μm in a material of density).[1,4] Therefore, the radiation intensity in a small capillary tissue unit is proportional to the DMI density (i.e., the flow).[26] Stochastic and methodological errors are considered insignificant because a large number of DMI molecules are deposited in one unit (i.e., one-pixel tissue size) without vascular embolization.

Study limitations

This study is rather descriptive, thereby documenting the myocardial flow heterogeneity in chronically hypoxic rats. Therefore, the underlying mechanism determining flow heterogeneity is beyond the scope of this study. Second, only relative flow distributions were evaluated in this study. The simultaneous measurement of the coronary blood flow and echocardiography will provide better understanding what happens in regional myocardial flow under chronic hypoxia. In addition, the postnatal exposure to hypoxia for 8 weeks may be too short to reproduce chronically hypoxic myocardium. Finally, only resting conditions were studied. Measuring the flow heterogeneity at stress (e.g., cardioplegic cardiac arrest or β-receptor stimulations) is therefore expected to provide clinically relevant information.

Conclusions

The chronically hypoxic neonatal myocardium exhibits nearly normal regional flow heterogeneity in both the left and right ventricles. The reoxygenation of chronically hypoxic myocardium resulted in a significant decrease in regional flow heterogeneity. Elucidating the mechanism determining myocardial flow heterogeneity and its clinical implications under chronic hypoxia requires further studies under stress conditions, including evaluation of both cardiac function and coronary artery flow.

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References

1. Matsumoto T, Kajiya F. Microheterogeneity of myocardial blood flow. Basic Res Cardiol 2001;96:547–52.
2. Deussen A. Blood flow heterogeneity in the heart. Basic Res Cardiol 1998;93:430–8.
3. King RB, Bassingthwaighte JB, Hales JR, Rowell LB. Stability of heterogeneity of myocardial blood flow in normal awake baboons. Circ Res 1985;57:285–95.
4. Austin RE Jr, Smedira NG, Squiers TM, Hoffman JI. Influence of cardiac contraction and coronary vasomotor tone on regional myocardial blood flow. Am J Physiol 1994;266: H2542–53.
5. Matsumoto T, Goto M, Tachibana H, Ogasawara Y, Tsujioka K, Kajiya F. Microheterogeneity of myocardial blood flow in rabbit hearts during normoxic and hypoxic states. Am J Physiol 1996;270:H435–41.
6. Weiss HR, Neubauer JA, Lipp JA, Sinha AK. Quantitative determination of regional oxygen consumption in the dog heart. Circ Res 1978;42:394–401.
7. Austin RE Jr, Aldea GS, Coggins DL, Flynn AE, Hoffman JI. Profound spatial heterogeneity of coronay reserve: discordance between patterns of resting and maximal myocardial blood flow Circ Res 1990;67;319–31
8. Najm HK, Wallen WJ, Belanger MP, Williams WG, Coles JG, Van Arsdell GS, et al. Does the degree of cyanosis affect myocardial adenosine triphosphate levels and function in children undergoing surgical procedures for congenital heart disease? J Thorac Cardiovasc Surg 2000;119:515–24.
9. Tajima M, Katayose D, Bessho M, Isoyama S. Acute ischaemic preconditioning and chronic hypoxia independently increase myocardial tolerance to ischaemia. Cardiovasc Res 1994;28:312–9.
10. Rabinovitch M, Gamble WJ, Miettinen OS, Reid L. Age and sex influence on pulmonary hypertension of chronic hypoxia and on recovery. Am J Physiol 1981;240:H62–72.
11. Matsumoto T, Ebata J, Tachibana H, Goto M, Kajiya F. Transmural microcirculatory blood flow distribution in right and left ventricular free walls of rabbits. Am J Physiol 1999;277:H183–91.
12. Hudlicka O, Brown M, Egginton S. Angiogenesis in skeletal and cardiac muscle. Physiol Rev 1992;72:369–417.
13. Marshall JM. Roles of adenosine and nitric oxide in skeletal muscle in acute and chronic hypoxia. Adv Exp Med Biol 2001;502:349–63.
14. DeFilippis AP, Law K, Curtin S, Eckman JR. Blood is thicker than water: the management of hyperviscosity in adults with cyanotic heart disease. Cardiol Rev 2007;15:31–4.

15. Kontras SB, Bodenbender JG, Craenen J, Hosier DM. Hyperviscosity in congenital heart disease. J Pediatr 1970;76:214–20.
16. Katayama Y, Horigome H, Murakami T, Takahashi-Igari M, Miyata D, Tanaka K. Evaluation of blood rheology in patients with cyanotic congenital heart disease using a microchannel array flow analyzer. Clin Hemorheol Microcirc 2006;35:499–508.
17. Asano T, Matsumoto T, Tachibana H, Takemoto M, Kajiya F. Myocardial microvascular perfusion after transfusion of liposome-encapsulated hemoglobin evaluated in cross-circulated rat hearts using tracer digital radiography. J Artif Organs 2004;7:145–8.
18. Vicaut E, Hou X, Decuypere L, Taccoen A, Duvelleroy M. Red blood cell aggregation and microcirculation in rat cremaster muscle. Int J Microcirc Clin Exp 1994;14:14–21.
19. Daniell HB, Bagwell EE. Effects of high oxygen on coronary flow and heart force. Am J Physiol 1968;214:1454–9.
20. Liao JC, Kuo L. Interaction between adenosine and flow-induced dilation in coronary microvascular network. Am J Physiol 1997;272:H1571–81.
21. Silverman NA, Kohler J, Levitsky S, Pavel DG, Fang RB, Feinberg H. Chronic hypoxemia depresses global ventricular function and predisposes to the depletion of high-energy phosphates during cardioplegic arrest: implications for surgical repair of cyanotic congenital heart defects. Ann Thorac Surg 1984;37:304–8.
22. Friedli B, Haenni B, Moret P, Opie LH. Myocardial metabolism in cyanotic congenital heart disease studied by arteriovenous differences of lactate, phosphate, and potassium at rest and during atrial pacing. Circulation 1977;55:647–52.
23. Corno AF, Milano G, Samaja M, Tozzi P, von Segesser LK. Chronic hypoxia: a model for cyanotic congenital heart defects. J Thorac Cardiovasc Surg 2002;124:105–12.
24. Nakanishi K, Inoue M, Sugawara E, Sano S. Ischemic and reperfusion injury of cyanotic myocardium in chronic hypoxic rat model: changes in cyanotic myocardial antioxidant system. J Thorac Cardiovasc Surg 1997;114:1088–96.
25. Van Arsdell GS, Maharaj GS, Tom J, Rao VK, Coles JG, Freedom RM, et al. What is the optimal age for repair of tetralogy of Fallot? Circulation 2000;102(suppl 3):III123–9.
26. Little SE, Link JM, Krohn KA, Bassingthwaighte JB. Myocardial extraction and retention of 2-iododesmethylimipramine: a novel flow marker. Am J Physiol 1986;250:H1060–70.

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Echocardiography

Transcatheter Closure of a Large Atrial Septal Defect under Microprobe Transesophageal Echocardiographic Guidance

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We present a case of an atrial septal defect (ASD) in a 59-year-old man with an indication for ASD closure who also had a history of chronic obstructive pulmonary disease. Because of his decreased respiratory function with multiple bullae in his lungs, the procedure was performed without general anesthesia under the guidance of fluoroscopy and two-dimensional (2D) transesophageal echocardiography (TEE) using a transesophageal echocardiographic microprobe (micro-TEE) (S8-3t; Philips Medical Systems, Andover, MA, USA). The micro-TEE probe was inserted into the esophagus smoothly and easily in the supine position without sedation. It revealed a deficient superior-anterior rim and adequate rims elsewhere, and the maximal diameter of ASD was measured to be 25 mm. Balloon sizing resulted in a stretched defect diameter of 29 mm using the stop-flow technique. A 30-mm AMPLATZER Septal Occluder (AGA Medical, Plymouth, MN, USA) was deployed. The micro-TEE demonstrated that both disks were on the appropriate sides of the interatrial septum and the device was not interfering with surround cardiac structures. Residual shunt flow was not detected with color Doppler. The device was released successfully without any complications. Recently introduced multiplane micro-TEE can provide adequate information about a large ASD with a less invasive procedure in adult patients. Micro-TEE has a potential to become a novel imaging option for interventions of the interatrial septum. (Echocardiography 2012;29:E94-E96)

Key words: transesophageal echocardiography, atrial septal defect, transcatheter closure device

A 59-year-old man with a history of chronic obstructive pulmonary disease who presented with progressive exertional dyspnea was found to have a secundum-type atrial septal defect (ASD) and a dilated right ventricle on transthoracic echocardiography (TTE). He was referred to our hospital for evaluation and transcatheter ASD closure.

Right heart catheterization demonstrated a pulmonary-to-systemic flow ratio of 1.8:1. His respiratory function was decreased due to multiple bullae in his lungs. And an intracardiac echocardiography was unavailable in our hospital. Therefore, transcatheter ASD closure was performed without general anesthesia under the guidance of fluoroscopy and two-dimensional (2D) transesophageal echocardiography (TEE) using a transesophageal echocardiographic microprobe (micro-TEE) (S8-3t; Philips Medical Systems, Andover, MA, USA) (Fig. 1). No sedatives were used, and local pharyngeal anesthesia was induced with oral liquid containing lignocaine. The micro-TEE probe was inserted into the

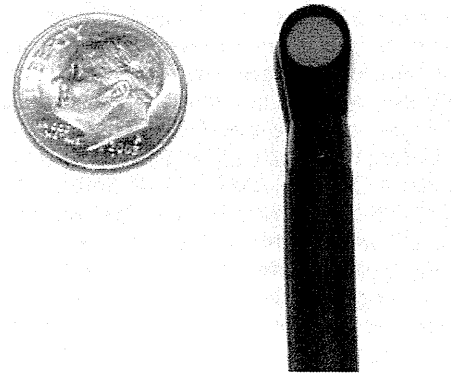

Figure 1. Miniaturized micro-TEE probe.

There are no disclosures about this report.

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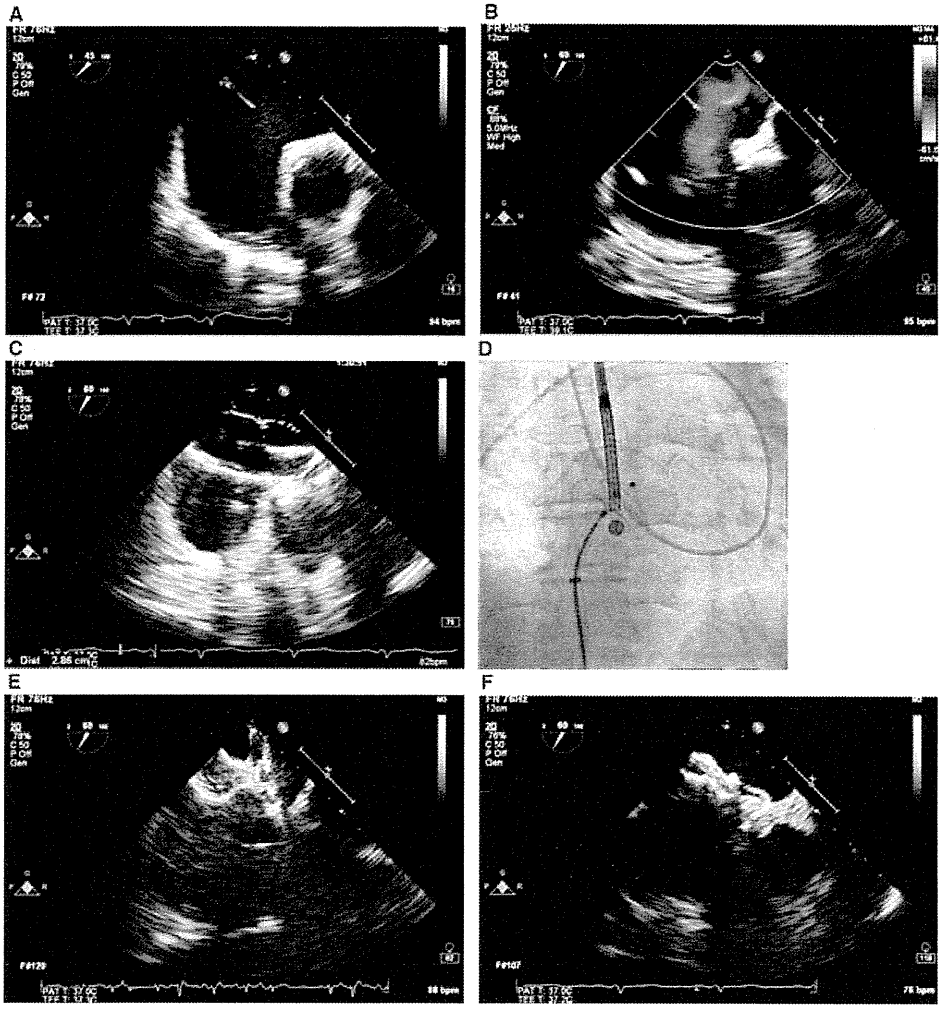

Figure 2. Transcatheter atrial septal defect closure under micro-TEE and fluoroscopic guidance. **A.** Micro-TEE demonstrates a large atrial septal defect (ASD) and a deficient superior-anterior rim. **B.** With color Doppler image, left-to-right shunt flow is recognized. **C.** Balloon sizing using the stop-flow technique **D.** Fluoroscopic view and **E.** micro-TEE view deploying a 30-mm AMPLATZER Septal Occluder **F.** Device is deployed successfully.

esophagus smoothly and easily in the supine position. It revealed a deficient superior-anterior rim and adequate rims elsewhere (Fig. 2A and B, movie clip S1), and the maximal diameter of ASD was measured to be 25 mm. Balloon sizing with a 34-mm AGA balloon (AGA Medical, Plymouth, MN, USA) resulted in a stretched defect diameter of 29 mm using the stop-flow technique (Fig. 2C). A 12-French AGA sheath was used to deliver the device. A 30-mm AMPLATZER Septal Occluder (AGA Medical, Plymouth, MN, USa) was deployed (Fig. 2D and E, movie clip S2). The micro-TEE clearly demonstrated that both disks were on the appropriate sides of the interatrial septum and the device was not interfering with surround cardiac structures. Residual shunt flow was not detected with color Doppler. The device was released successfully without any complications (Fig. 2F).

The extremely miniaturized multiplane micro-TEE has 18.5 mm of tip length, 7.5 mm of tip width, and 5.5 mm of tip height. The shaft size is 5.2 mm which is about a half size of the standard TEE probe for adults. The transducer consisted of 32 elements and has frequency from 3.2 MHz to 7.4 MHz. 2D, as well as M-mode, color Doppler, pulse-wave wave Doppler, and continuous-wave Doppler are available.

Echocardiography plays a pivotal role in guiding interventions of structural heart diseases. There are several imaging tools of echocardiographic guidance for structural heart interventions including 2D TTE, 2D TEE,[1] intracardiac echocardiography,[2,3] and recently introduced

real-time three-dimensional (3D) TEE.[4,5] From the standpoint of echocardiographic options for transcatheter closure of an interatrial septum in the catheterization laboratory, the small size of the micro-TEE probe may be better tolerated without general anesthesia for a prolonged procedure such as ASD closure, as compared to a standard TEE probe. In addition, micro-TEE has some advantages compared to intracardiac echocardiography in terms of capability of multiplane, reusability, avoiding vascular complications and cost effectiveness. However, image quality of the current micro-TEE probe is inferior to that of a conventional adult TEE probe, and inability of 3D imaging by a micro-TEE probe can also be a limitation.

Micro-TEE could provide adequate information with a less invasive procedure even in patients with a large ASD. Micro-TEE has the potential to become a novel imaging option for interventions of the interatrial septum.

References

1. Mazic U, Gavora P, Masura J: The role of transesophageal echocardiography in transcatheter closure of secundum atrial septal defects by the Amplatzer septal occluder. *Am Heart J* 2001;142:482–488.
2. Kim SS, Hijazi ZM, Lang RM, et al: The use of intracardiac echocardiography and other intracardiac imaging tools to guide noncoronary cardiac interventions. *J Am Coll Cardiol* 2009;53:2117–2128.
3. Ali S, George LK, Das P, et al: Intracardiac echocardiography: Clinical utility and application. *Echocardiography* 2011;28:582–590.
4. Taniguchi M, Akagi T, Watanabe N, et al: Application of real-time three-dimensional transesophageal echocardiography using a matrix array probe for transcatheter closure of atrial septal defect. *J Am Soc Echocardiogr* 2009;22:1114–1120.
5. Eng MH, Salcedo EE, Quaife RA, et al: Implementation of real time three-dimensional transesophageal echocardiography in percutaneous mitral balloon valvuloplasty and structural heart disease interventions. *Echocardiography* 2009;26:958–966.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Movie clip S1: Short-axis view with micro-TEE shows a large atrial septal defect (ASD) and a deficient superior-anterior rim.

Movie clip S2: The micro-TEE shows that both disks are on the appropriate sides of the interatrial septum.

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