Acute Rupture of Chordae Tendineae of the Mitral Valve in Infants
A Nationwide Survey in Japan Exploring a New Syndrome

Running title: Shiraishi et al.; Rupture of mitral chordae tendineae in infants

Isao Shiraishi, MD, PhD1; Kunihiro Nisihmura, MD, PhD2; Heima Sakaguchi, MD, PhD1; Tadaaki Abe, MD, PhD1; Masataka Kitano, MD1; Kenichi Kurosaki, MD1; Hitoshi Kato, MD, PhD3; Toshio Nakanishi, MD, PhD4; Hiroyuki Yamagishi, MD, PhD5; Koichi Sagawa, MD6; Yoshihiko Ikeda, MD7; Takayuki Morisak, MD, PhD8; Takaya Hoashi, MD, PhD9; Koji Kagisaki, MD9; Hajime Ichikawa, MD, PhD9

1Dept of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Osaka; 2Dept of Preventive Cardiology, National Cerebral and Cardiovascular Center, Osaka; 3Dept of Cardiology, National Center for Child Development and Growth, Tokyo; 4Dept of Pediatric Cardiology, Tokyo Women’s Medical University, Tokyo; 5Dept of Pediatrics, Keio University School of Medicine, Tokyo; 6Dept of Cardiology, Fukuoka Children’s Hospital, Fukuoka; 7Dept of Clinical Pathology, National Cerebral and Cardiovascular Center, Osaka; 8Dept of Bioscience and Genetics, National Cerebral and Cardiovascular Center, Osaka; 9Dept of Pediatric Cardiac Surgery, National Cerebral and Cardiovascular Center, Osaka, Japan

Address for Correspondence:
Isao Shiraishi, MD, PhD
Department of Pediatric Cardiology
National Cerebral and Cardiovascular Center
5-7-1, Fujishirodai
Suita, Osaka, Japan 565-8565
Tel: +81-6-6833-5012
Fax: +81-6-6835-5256,
E-mail: shiraishi.isao.hp@ncvc.go.jp

Journal Subject Code: Cardiovascular (CV) surgery:[41] Pediatric and congenital heart disease, including cardiovascular surgery
Abstract

**Background**—Recently, infant cases of acute heart failure due to rupture of the mitral chordae tendineae have been reported. However, little is known about the pathogenesis and clinical course of this condition.

**Methods and Results**—Ninety-five children with rupture of mitral chordae tendineae were identified in nationwide surveys of Japan diagnosed from 1995 to 2013. The clinical manifestations, management strategies and prognosis were investigated. Eighty-one (85%) patients were between 4 and 6 months (median: 5 months) of age. In 63 (66%) patients, rupture occurred during the spring or summer. The underlying conditions before rupture included Kawasaki disease (10 cases), maternally derived anti-SSA antibodies (two cases) and infective endocarditis (one case). Surgery was performed in 80 patients (94 operations), and the final operations included plasty of mitral chordae in 52 cases and mechanical valve replacement in 26 cases. The histopathological examinations of the mitral valves and chordae (n=28) revealed inflammatory reactions with predominant mononuclear cell infiltration in 18 cases (64%) and increased fibrous and myxoid tissue in 11 cases (39%), suggesting that non-bacterial infectious or autoimmune endocarditis and myxoid changes are involved in the pathogenesis. Eight patients (8.4%) died before (n=6) and shortly after (n=2) the operation, and significant neurological complications persisted in 10 cases (11%).

**Conclusions**—Acute heart failure due to rupture of the mitral chordae tendineae in infants is a unique disease resulting from diverse etiologies. This condition should be recognized as a significant cardiovascular disorder that may cause sudden onset of cardiogenic shock and death in infants.

**Key words:** pediatrics, acute heart failure, mitral regurgitation, cardiovascular pathophysiology
Acute massive mitral regurgitation due to rupture of the chordae tendineae is a serious condition in which the patient suffers from the sudden onset of circulatory and respiratory failure.\textsuperscript{1-3} This disease generally occurs in older children, adolescents and adults, and the underlying conditions are diverse;\textsuperscript{2,3} for example, myxomatous change of the mitral valve,\textsuperscript{3} systemic connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome,\textsuperscript{2,4,5} infectious endocarditis,\textsuperscript{2,6,7} rheumatic fever,\textsuperscript{2,3,8,9} hypertension,\textsuperscript{10,11} labor and delivery,\textsuperscript{12} blunt chest trauma,\textsuperscript{2,13} and abnormalities of mitral apparatus such as single papillary muscle or double orifice mitral valve.\textsuperscript{14,15}

Until recently, rupture of the mitral chordae tendineae was thought to be rare in young children. However, several child cases without congenital malformations of mitral valve apparatus have been reported in Japan, with the majority of cases, interestingly, being in infants.\textsuperscript{16-22} According to the literature, the prognosis of affected patients is, in general unsatisfactory, as a number of patients were treated with mechanical valve replacement and several patients died of cardiogenic shock.\textsuperscript{19,20} To make matters worse, the clinical entities and criteria of the disease have not been described in any textbook of pediatrics or pediatric cardiology. Consequently, pediatricians, and even pediatric cardiologists, do not know much about the disease.

In order to elucidate the etiology, clinical manifestations, appropriate medical and surgical treatment and prognosis of the disease, we conducted a nationwide retrospective survey of acute rupture of the chordae tendineae of the mitral valve in children in Japan. Although the cases reported here are limited to Japanese infants, this disease does occur in other countries. Some patients may have gone unnoticed after dying or being misdiagnosed with other conditions such as sudden infant death syndrome. Therefore, acute rupture of the mitral chordae tendineae
in infants is a new disease entity and should be recognized as a significant cardiovascular disorder that may cause sudden onset of cardiogenic shock and death.

**Methods**

**Study Patients**

This study is a retrospective cohort study of acute rupture of the mitral chordae tendineae in children occurring between July 1995 and August 2013. A primary questionnaire was sent to 532 clinical training hospitals approved by the Japanese Society of Pediatrics, requesting information on cases of children (under 15 years of age) with rupture of the mitral chordae between 1995 and 2013. Two hundred and fifty-two hospitals (56.3%) responded to the first questionnaire, 64 (12.0%) hospitals gave affirmative responses to such cases. The second questionnaire was forwarded to the 64 institutes, inquiring about clinical manifestations, medical and surgical treatments and prognoses of patients. Ninety-five cases were investigated in the study. Seventeen cases previously reported \(^{17,19,20,22}\) were included in this nationwide survey. The diagnosis of Kawasaki disease was conducted by Board Certified Pediatricians of each hospital according to the diagnostic guidelines for Kawasaki disease. \(^{23,24}\) The institutional review committee of National Cerebral and Cardiovascular Center approved the study.

**Pathological Diagnosis and Immunohistochemistry**

A pathologist at the National Cerebral and Cardiovascular Center examined the actual specimens in 13 of 28 cases, whereas the study group relied on written documents and microphotographs of the specimens in the 15 remaining cases reported by board certified pathologists at each institute. The immunohistochemistry procedures for tenascin C (mouse monoclonal, clone: 4F10TT, dilution 1:1,000; Immuno-Biological Laboratories, Inc.), CD3 (rabbit polyclonal, dilution 1:10;
Dako Japan Inc.), and CD68 (mouse monoclonal, clone: KP-1, dilution 1:1,000; Dako Japan Co., Ltd.) were performed on formalin-fixed, paraffin-embedded chordal sections using an established method. All the immunohistochemical studies were performed in the department of pathology, National Cerebral and Cardiovascular Center.

**Statistical Analysis**

The data of the patients are presented as the median with interquartile range values for continuous demographic variables and laboratory findings. The Wilcoxon signed rank test was used to compare the laboratory data obtained at the onset of symptoms and discharge from the hospital because of the skewed nature of distribution. For the rate of pulmonary congestion, McNemar’s test was conducted. Cumulative event-free survival curves were estimated using the Kaplan-Meier method. Cox proportional hazards models were used to identify factors associated with the time to aortic valve replacement and time to death. Hazard ratios and 95% confidence intervals were also estimated. *P* value of <0.05 was considered to be statistically significant.

**Results**

**Clinical Features of the 95 Patients**

A typical case of acute rupture of the mitral chordae tendineae is shown in Figure 1. A 4-month-old female infant without a history of significant illnesses exhibited the sudden onset of a cyanosis and dyspnea following two days of fever. The initial diagnosis was pneumonia (Figure 1A); however, severe mitral regurgitation and rupture of the chordae tendineae were diagnosed in secondary and tertiary hospitals, respectively (Figure 1B, C). Surgical repair using artificial chordae was performed in association with mitral annuloplasty (Figure 1D). The intraoperative findings demonstrated that four chordae tendineae on the posterior leaflet were lacerated. After
surgery, severe regurgitation successfully reduced to a trivial level.

The clinical characteristics of 95 patients are shown in Table 1 and Figure 2. There were 52 males and 43 females (Figure 2A) and ages ranged from 21 days to 16 months after birth (median: 5 months, Figure 2B). The majority of patients were infants: 81 patients (85%) were between 4 to 6 months of age (Figure 2C), with body weight of 6.83 kg. Patients were born at 39 gestational weeks (median), with a body weight of 2.96 kg. Apgar score at one minute after birth was 9 (interquartile range: 8-10), indicating that perinatal asphyxia with myocardial ischemia was not an underlying condition of rupture. Diagnosis of Kawasaki disease was made in 10 patients (11%) before the onset of the rupture; acute and convalescent stage in 3 patients and beyond convalescent stage in 7 patients. The remaining 85 patients did not meet the clinical criteria for Kawasaki disease. In one patient (a 5-month-old, female), Staphylococcus epidermidis endocarditis was diagnosed by positive blood culture tests and histopathological examinations of the resected mitral valve.

Next, we analyzed seasonal epidemics of the disease (Figure 2B). The disease had a seasonal epidemic in spring and summer (65 patients, 68%). There were no sibling cases in this study. Most patients exhibited prodromal symptoms such as fever or cough 3.5 days before admission. Symptoms of cardiorespiratory shock developed 2.0 days after the onset of the prodroms. None of the 95 patients displayed any clinical symptoms of group A streptococcal infection or clinical signs of rheumatic fever. Clinical features of Marfan syndrome such as scoliosis, arachnodactyly, and pectus carinatum/excavatum were not found in patients. No evidence of blunt chest trauma was found in any of the patients.

Laboratory Findings

The results of the laboratory examinations are summarized in Table 2. On admission, white
blood cell count increased (median: 15,440 /uL) and serum C-reactive protein concentration had a slight increase (1.60 mg/dL). However, the procalcitonin level, which is a sensitive marker of bacterial infection, remained at a normal value (0.025 ng/mL, n=4). Although the disease provoked systemic inflammatory reactions, these data suggest that bacteremia was unlikely to be a major etiology of the condition.

A marked increase in the brain natriuretic protein (BNP) level (1,450 pg/ml) and an elevated lactate level (4.43 mg/dl, n=36) on admission indicates that the majority of patients suffered from acute cardiac and circulatory failure. Serum levels of creatine kinase-myocardial band (CK-MB) and cardiac troponin T (cTnT) were not significantly elevated, suggesting that prominent myocardial cell damage was not related to the disease.

Maternally derived anti-SSA antibodies, which are a well-known cause of conduction tissue disturbances and myocardial cell damage during the fetal period,26-28 were detected in two of the 12 patients examined (21 days and 5 months after birth). In these cases, no signs of complete atrioventricular block or systolic dysfunction were detected. Only elongation of the PQ interval was found in the neonate. No other antinuclear antigens such as anti-SSB, anti-ANF, or anti-DNA, were detected in the ten patients examined.

As most patients were in an emergent condition, isolation of viruses and paired serum examinations for virus antibody titers were not examined. Antibody against Human Immunodeficiency Virus, which may cause non-bacterial thrombotic endocarditis, was not detected in all cases.

**Chest X-ray, ECG and Echocardiography Findings**

Although bilateral pulmonary congestion was recorded in 71 patients (75%), cardiomegaly was not evident; the median cardio-thoracic ratio in chest X-ray was 56 (51-59)%. In the majority of
patients, electrocardiograms revealed non-specific ST-T changes in the precordial leads, which had normalized by the time of discharge. No abnormal Q waves were recorded in any of the patients.

The diagnosis of rupture of the mitral chordae was confirmed on echocardiography. Fractional shortening ((LV end-diastolic diameter – LV end-systolic diameter)/(LV end-diastolic diameter)) of the left ventricle on admission was seemingly high (median: 0.41 (0.36-0.46)). Doppler echocardiography on admission showed severe mitral regurgitation in 70 patients (73%), moderate in 22 (23%), and mild in 4 (4%). To exclude the possibility that preceding chronic mitral regurgitation induced the rupture, end-diastolic diameter (BSA indexed) z-score of the left ventricle was assessed. The median value of the z-score was 1.47, indicating that the rupture is an acute event. A noteworthy echocardiographic finding was the presence of high echoic lesions at the top of the mitral papillary muscle adjacent to the chordae (8 patients, 8.4%). Abnormal thickening of the mitral valve leaflets was also detected in nine patients (9.5%). No coronary artery aneurysms or abnormal origins of the left coronary arteries were detected. Dilatation of aortic root was not detected, either.

**Surgical Treatment**

A total of 95 surgical operations (Figure 3) were performed upon 80 patients (84%). Plasty of the mitral apparatus included reinforcement of the ruptured chordae with autologous pericardium, suture of the lacerated mitral valve leaflet, and mitral valve annuloplasty (57 patients). Twenty-six mechanical valves (16-19mm in diameter) were implanted. In nine patients, mitral regurgitation deteriorated after the surgical repair, primarily due to newly emerged rupture of the chordae tendineae. Although mitral regurgitation remained after the surgical repair, significant mitral stenosis was noted only in one patient (RV/LV pressure=0.86), who is a
candidate for mechanical valve replacement.

In 83 patients, the details of the portions of the ruptured mitral chordae were recorded in the clinical charts. Rupture in one, two, three and four portions was noted in 38, 33, nine and three patients, respectively. Rupture of the anterior leaflets alone, the posterior leaflet alone, and both leaflets was identified in 28, 33, and 22 patients, respectively. Thickened and myxoid mitral valve leaflets were identified in 13 patients at the time of surgery. No vegetation on the mitral valve apparatus was detected.

Rupture of the chordae tendineae of the tricuspid valve was detected in six patients; five patients survived after chordae repair, and one patient died before undergoing surgery. In nine patients, surgical repair was not performed because the mitral regurgitation was limited in the small area and the patients became asymptomatic after medical treatment. These patients were carefully followed up with echocardiography and medical treatment, including diuretics and angiotensin-converting enzyme inhibitors.

**Histopathological Findings**

Macroscopic (Figure 4A) and histopathological examinations (Figures 4B-4L) of the mitral chordae and/or valves were performed in 28 patients. In the majority of patients, mononuclear cells had infiltrated the endocardium of the mitral valve leaflets and chordae tendineae (18 patients, 64%; Figure 4B and 4C). Polymorphonuclear leukocyte infiltration was also detected in the inflammatory lesions (Figure 4C); however, the number of polymorphonuclear leukocytes was far less than that of mononuclear cells. Ruptured portions were replaced by scar formation with fibrin deposition and fibrous tissue (Figure 4D, 4E). Myxoid change of the mitral valve leaflets and chordae tendineae was detected in 11 patients (39%, Figures 4F). Thickening of the spongiosa accompanied by infiltration of the fibrous component was also identified (Figure 4G).
Immunohistochemical examinations revealed that tenascin C, a characteristic component of the extracellular matrix during embryonic development, inflammatory reactions and tissue repair, was expressed in all layers of chordal tissue (Figure 4J). Immunohistochemical study revealed that infiltrated mononuclear cells consisted of CD3-positive T-lymphocytes (Figure 4K) and CD68-positive macrophages (Figure 4L).

In a 5-month-old female with Staphylococcus epidermidis-positive blood culture tests, predominant polymorphonuclear leukocyte infiltration was identified and she was diagnosed with bacterial endocarditis. None of the specimens showed any histopathological characteristics of rheumatic endocarditis. Histopathological examinations of the two autopsied cases revealed no obvious infiltration of inflammatory cells in the ventricular myocardium. No inflammatory reactions were detected in any other organs, such as the liver, kidneys and gastrointestinal tract. Biopsy specimens were not obtained in the two patients with positive anti-SSA antibodies.

**Prognosis**

Eight patients (8.4%) died of circulatory failure and/or multiple organ dysfunctions (2 male and 6 female; 6 before surgery and 2 after surgery). The median ages of the eight patients was 4 months. All six patients who died before surgery exhibited serious cardiorespiratory failure at the initial stage of shock and were immediately transferred to a tertiary care hospital. After the surgical repair and/or medical treatment, the patients were discharged from the hospital with normal left ventricular FS values in echocardiography (0.36). During the three months to 18 years of follow-up (median: 5.4 years), mitral regurgitation persisted in nine patients; five cases were slight and four cases were moderate. The left ventricular FS at present were almost within normal limits (median: 0.37, range 0.24-0.57). Only three patients showed impaired echocardiographic FS less than 0.28 (0.24, 0.25 and 0.26). The BNP levels at presentation were
within normal range (median: 34.8 pg/ml).

Neurological complications, such as significant developmental delays and/or cerebral palsy, were detected in 10 patients (11%, 95% CI 4.2% -14.1%). As a whole, significant complications remained in 32 patients (34%; mitral replacement in 26, neurological complications in 10, both in 4), indicating a mortality and morbidity of the disease of 8.4% (95%CI 2.73-14.1) and 42% (95%CI 32.0%-52.2%), respectively.

Forty-eight (51%, 95% CI 40.3%-60.8%) patients continue to take drugs, i.e., angiotensin-converting enzyme inhibitors in 31 patients, diuretics in 22 patients, coumadin in 29 patients, antiplatelet drugs in 17 patients and anti-arrhythmia drugs in three patients. At present, arrhythmias persist in eight patients (8.4%, 95% CI 2.7% -14.1%), including atrial flutter in three patients, atrial tachycardia in two patients and complete atrioventricular block with pacemaker implantation in three patients. All arrhythmias are well controlled with medication.

Factors Associated with Artificial Valve Replacement and Death
In order to detect predictors of artificial valve replacement and death in the patients, the cumulative probability of freedom from artificial valve replacement was analyzed according to the Kaplan-Meier method (Figure 5). The probability of artificial valve replacement-free survival was lower among the patients who developed chordal rupture in summer than among those who developed this complication in other seasons (Figure 5A). The artificial valve replacement-free survival was also lower in the patients who developed 3-4 chordae than in those who developed 1-2 chordae (Figure 5B). Significant predictors of artificial valve replacement identified in the Cox proportional hazard models are shown in Table 3. Rupture in the summer and the number of ruptured chordae tendineae were significantly associated with the risk of artificial valve replacement. In contrast, no significant clinical or laboratory factors were
associated with the risk of death in the univariable analyses.

Discussion

Rupture of the chordae tendineae of the mitral valve in infants is rare. The majority of affected patients present with the sudden onset of severe cardiorespiratory shock. Some patients die, while others require urgent surgical treatment, such as mitral chordae plasty or mechanical valve replacement. In infants treated surgically with prosthetic valves, reoperation to "up-size" the valves is likely to be necessary as the patients grow, depending on the size of initial prosthesis. In order to improve the prognosis of these patients, providing an early diagnosis, appropriate medical treatment and successful surgery is crucial. Since the disease is not currently recognized worldwide, some patients may have remained undiagnosed or been misdiagnosed. Some cases may have occurred in other countries as well. Therefore, acute rupture of the mitral chordae tendineae needs to be considered a significant cardiac disease that may cause sudden onset of acute cardiac failure in infants.

Etiologies of the Disease

In adolescents and adults, the underlying etiologies of the rupture of the chordae tendineae are diverse; mitral valve prolapse, myxomatous degeneration, and infectious endocarditis are the leading causes particularly in the last two decades. In infants, etiologies of the rupture appear to be different from those in adults; most pediatric cases of mitral rupture were diagnosed as "idiopathic" since a direct cause could not be demonstrated. In a small number of cases, Kawasaki disease, a child-specific etiology was the documented cause for this condition. Rupture of the mitral chordae or papillary muscles may occur in Kawasaki disease after myocardial ischemia or infarction of the ventricular inferior wall. Mitral regurgitation without coronary
arterial lesions may also occur during the acute or convalescent stage of Kawasaki disease, in which the histopathological findings indicate the involvement of endocarditis and valvulitis.\textsuperscript{31-33} In our patients, no signs of myocardial ischemia or infarction were detected. Endocarditis or valvulitis in Kawasaki is a potential cause of the chordal rupture.

The actions of maternally derived anti-SSA/SSB antibodies appear to reflect another child specific pathogenesis particularly in neonates and early infancy. The transplacental passage of antibodies against SSA or SSB auto-antigens has been proven to be an etiology of congenital complete atrioventricular block in neonates.\textsuperscript{26-28} Dilated cardiomyopathy or endocardial fibroelastosis may also develop as a late-onset cardiac complication.\textsuperscript{34} Molecular studies have clarified that these antibodies initially bind to the L-type calcium channel on fetal cardiomyocytes, where they induce calcium dysregulation, apoptosis, inflammation and subsequent conduction tissue disturbance.\textsuperscript{35} Echocardiography has demonstrated high echoic lesions at the top of the papillary muscles.\textsuperscript{17} Obviously, these findings have to be distinguished from “echogenic intracardiac focus” in the normal fetus.\textsuperscript{36} Similar cellular mechanisms may be involved, where fibrous scar formation develops during the fetal period and subsequent rupture may occur early after birth.

Myxoid change of the mitral valve leaflets and chordae tendineae was detected in 39\% of available specimens. Histological examinations revealed abnormal deposition and disorganization of collagen and elastin and accumulation of proteoglycans in the myxoid mitral valve with ruptured chordae tendineae\textsuperscript{37}, suggesting that these histological changes are the predisposing cause of the rupture. Since changes in the structure of the mitral leaflets such as those seen in myxomatous degeneration take time to develop, further studies are necessary to elucidate the contribution of myxoid change to mitral chordal rupture in infants.
Indirect evidence supports the theory of an infectious or para-infectious inflammatory etiology in many cases: 1) inflammatory cells were detected on the histochemistry analysis in 69% of available specimens; 2) prodromal symptoms similar to viral infections; 3) seasonal epidemics having peaked in summer; 4) high incidence in the middle of infancy when maternal antibodies become undetectable, and 5) lymphocyte predominant infiltration in the specimen. As the presence of inflammatory cells involving the ruptured chordae may have developed as a consequence of rupture rather than be a causal factor, further studies including the detection of viral genomes and isolation of viruses are being considered.

Lastly, why acute mitral chordal rupture in infants is predominant in the Japanese population remains uncertain. In countries other than Japan, this condition seems to be rare, as no cases other than one case of an anti-SSA antibody-positive infant \(^{18}\) have been described in literature thus far. Some genetic background factors appear to be responsible for the disease, as Kawasaki disease is dominant in Japanese and Asian children. Further studies are therefore needed to elucidate the genetic susceptibility of the disease.

**Medical and Surgical Treatment**

The initial treatment should include medical support, such as the intravenous infusion of inotropes, diuretics and vasodilators and mechanical ventilation with tracheal intubation. If the circulatory and respiratory failure is uncontrollable, surgical repair of the ruptured chordae tendineae should be immediately considered. Plasty of the lacerated chordae using reinforcement with or without artificial chordae is the first choice of surgery \(^{20-22}\) as mechanical valve replacement in infancy always requires upsizing reoperation as the patient ages. \(^{38}\) However, if the rupture includes multiple, particularly 3 or more chordae, a risk factor for mechanical valve replacement, and is difficult to repair with the plasty technique, mechanical valve replacement
should be considered.20-22

**Study Limitations**

There are several limitations to this study. First, this study was based on a retrospective nationwide survey of mitral chordal rupture in Japan. Due to the emergent condition of each patient, data concerning clinical manifestations and laboratory findings particularly relevant to the pathogenesis were not satisfactory. Specimens for histochemistry were available in only 28 of 95 patients (presumably weighted towards the most serious cases requiring valve replacement and/or resulting in death), thus limiting the generalizability of the histological findings to the whole group. Further nationwide prospective studies are therefore essential, including isolation of viruses and investigation of virus genome from blood and tissues samples. Second, appropriate medical and surgical therapy to prevent the progression of rupture has not yet been established. Prospective studies concerning additional medical and surgical treatment are also necessary. Third, this study was conducted in Japanese children only. Although the possible etiologies are diverse and various ethnic or genetic background factors are likely responsible, it is highly possible that this disease develops in countries other than Japan. Worldwide surveys are needed to clarify the incidence, pathogenesis and prognosis of the disease.

**Conclusions**

Acute rupture of the mitral chordae tendineae in infants is a unique disease that predominantly affects patients 4-6 months of age, with high mortality and morbidity. Kawasaki disease, maternally derived anti-SSA antibodies, myxoid change of the mitral valve and lymphocytic endocarditis are possible candidate causes of the chordal rupture; however, precise etiology is uncertain and the patients are diagnosed with idiopathic. Although the reason why the disease is
predominant in Japanese infants remains to be elucidated, acute rupture of the mitral chordae tendineae should be recognized as a significant cardiovascular disorder that may cause sudden onset of cardiogenic shock or death in infants all over the world.

**Funding Sources:** This study was supported by research grants from the Japanese Ministry of Health, Labor and Welfare (H22-intractable diseases-general-031, H25-intractable diseases-general-010) and a research grant from the Japanese Ministry of Education, Culture, Sports, Science and Technology (25140101).

**Appendix**

**List of Investigators and Participating Centers**

Masato Yokosawa, MD, Hokkaido Medical Center for Child Health and Rehabilitation; Michihiko Ueno, MD, Atsuhito Takeda, MD, Hokkaido University Hospital; Eiichiro Hatta, MD, Keijinkai Teine Hospital; Toshio Ohara, MD, Tomakomai City Hospital; Kotaro Oyama, MD, Mika Sasaki, MD, Iwate Medical University; Yoichi Murakami, MD, Kitakami Saiseikai Hospital; Shuhei Kakizaki, MD, Tohoku University Hospital; Tomio Kobayashi, MD, Gunma Children's Medical Center; Hirohiko Shiraishi, MD, Jichi Medical University Hospital; Tatsuo Tsuboi, MD, Dokkyo University Hospital; Kiyoshi Ogawa, MD, Saitama Children's Medical Center; Masaru Miura, MD, Tokyo Metropolitan Children's Medical Center; Masahiro Otsuka, MD, Tokyo Metropolitan Bokuto Hospital; Kei Inai, MD, Tokyo Women's Medical University Hospital; Keiko Sato, MD, Juntendo University Hospital; Takashi Urashima, MD, Jikei University Hospital; Mikage Arata, MD, Tokyo Medical University Hospital; Shoji Matsumura, MD, Mamoru Ayusawa, MD, Nihon University Itabashi Hospital; Hiroko Asakai, MD, National Center for Child Health and Development; Takashi Nishizawa, MD, Yokohama City University Hospital; Hideaki Ueda, MD, Kison Kim, MD, Kanagawa Children's Medical Center; Yoichi Kaburaki, MD, National Hospital Organization Yokohama Medical Center; Masahiro Ishii, MD, Yayoi Nakahata, MD, Kitasato University Hospital; Shinichi Matsuda, MD, Tokai University Hospital; Satoshi Yasukochi, MD, Nagano Children’s Hospital; Yasuo Ono, MD, Shizuoka Children's Hospital; Yoshiki Mori, MD, Yasumi Nakajima, MD, Seirei Hamamatsu General Hospital; Tomochika Kato, MD, Toyokawa City Hospital; Satoru Kawai, MD, Aichi Children's
Health and Medical Center; Satoko Hirano, MD, Yasunori Ishihara MD, Fukui Aiiku Hospital; Koichi Nishida, MD, Satoshi Tamura, MD, Fukui Cardiovascular Center; Kyoko Imanaka-Yoshida, MD, Mie University Graduate School of Medicine; Nobuhiko Okamoto, MD, Omihachiman Community Medical Center; Kentaro Toiyama, MD, Kyoto Prefectural University of Medicine Hospital; Naho Kobayashi, MD, Kyoto Second Red Cross Hospital; Ken Yoshimura, MD, Kansai Medical University Hirakata Hospital; Yoshihiro Miyamoto, MD, Shin Ono, MD, Wataru Tamaki, MD, Jun Negishi, MD, National Cerebral and Cardiovascular Center; Yosuke Murakami, MD, Osaka City General Hospital; Toru Shinohara, MD, Kinki University Hospital; Masahiko Matsumura, MD, Tenri Hospital; Toshiro Maihara, MD, Hyogo Prefectural Tsukaguchi Hospital; Masaru Yamakawa, MD, Kobe City Medical Center General Hospital; Toshikatsu Tanaka, MD, Hyogo Children's Hospital; Takashi Fukaya, MD, Nishikobe Medical Center; Yasunobu Hayabuchi, MD, Tokushima University Hospital; Naomi Nakagawa, MD, Kunikazu Hisamochi, MD, Hiroshima City Hiroshima; Kenji Yasuda, MD, Shimane University Hospital; Yasuo Suzuki, MD, Yamaguchi University Hospital; Takashi Higaki, MD, Ehime University Hospital; Hideaki Kado, MD, Fukuoka Children's Hospital; Yoshikazu Otsubo, MD, Sasebo City General Hospital; Junichi Takagi, MD, Miyazaki University Hospital

Conflict of Interest Disclosures: None.

References:


Table 1. Clinical Characteristics of the 95 patients.

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (months)</td>
<td>5 (4-6)*</td>
</tr>
<tr>
<td>Body weight at onset (kg)</td>
<td>6.83 (6.14-7.51)*</td>
</tr>
<tr>
<td>Gestational weeks</td>
<td>39 (38-40)*</td>
</tr>
<tr>
<td>Body weight at birth (kg)</td>
<td>2.97 (2.70-3.28)*</td>
</tr>
<tr>
<td>History of Kawasaki disease</td>
<td>10 cases; Acute and convalescent stage (day≤30), 3 cases Beyond convalescent stage (day&gt;30), 7 cases</td>
</tr>
<tr>
<td>Anti-SSA antibody-positive</td>
<td>2 cases; (12 cases examined) 0 and 5 months</td>
</tr>
<tr>
<td>Prodromal symptoms</td>
<td>88 cases; fever 37, cough 16, vomit 14, others 21</td>
</tr>
<tr>
<td>Cardiogenic shock after initial prodromes</td>
<td>2 (1-7) *</td>
</tr>
</tbody>
</table>

Data are presented as *median (interquartile range).

Table 2. Laboratory findings of the 95 patients.

<table>
<thead>
<tr>
<th>Examinations</th>
<th>On admission</th>
<th>At discharge</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (/uL)</td>
<td>15,440 (11,990-21,650)</td>
<td>9,160 (7,330-11,100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10.2 (8.9-11.1)</td>
<td>11.8 (10.9-13.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PLT (x10^3/uL)</td>
<td>501 (338-600)</td>
<td>368 (302-439)</td>
<td>0.0003</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.60 (1.97-3.15)</td>
<td>0.11 (0.16-0.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>44 (30-105)</td>
<td>36 (29-44)</td>
<td>0.0003</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>21 (13-135)</td>
<td>22 (16-36)</td>
<td>0.0160</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>421(267-763)</td>
<td>332 (264-484)</td>
<td>0.0046</td>
</tr>
<tr>
<td>CPK (IU/L)</td>
<td>119 (77-247)</td>
<td>76 (45-123)</td>
<td>0.0002</td>
</tr>
<tr>
<td>CPK-MB (U/L)</td>
<td>27 (12-91)</td>
<td>31 (20-42)</td>
<td>0.0749</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>1,450 (839-2,545)</td>
<td>72 (32-114)</td>
<td>0.0007</td>
</tr>
<tr>
<td>cTnT (n=22, ng/mL)</td>
<td>0.027 (0-0.132)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

Table 3. Univariable analyses of risk factors for mechanical valve replacement

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>z</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summer</td>
<td>2.44</td>
<td>2.26</td>
<td>0.024</td>
<td>1.12</td>
</tr>
<tr>
<td>Number of ruptured chordae</td>
<td>1.98</td>
<td>2.88</td>
<td>0.004</td>
<td>1.24</td>
</tr>
<tr>
<td>Number of ruptured chordae≥3</td>
<td>4.86</td>
<td>3.53</td>
<td>&lt;0.001</td>
<td>2.02</td>
</tr>
</tbody>
</table>

HR, hazard ratio; 95% CI, 95% Confidence interval.
Figure Legends:

Figure 1. Case presentation of acute rupture of the mitral chorda tendineae in an infant (a 5-month-old female). A. A chest X-ray shows pulmonary congestion with mild cardiomegaly (cardiothoracic ratio=0.60). B. An echocardiogram of the left parasternal long axis view demonstrating the severely prolapsed posterior leaflet of the mitral valve (arrow). C. A 2-D Doppler cardiogram showing severe mitral regurgitation and an enlarged left atrium. D. The operative record of the mitral valve and ruptured chordae tendineae. The arrows indicate ruptured chordae tendineae. The arrowhead indicates yellowish degeneration of the anterior mitral leaflet (AML). PML; posterior mitral leaflet.

Figure 2. Clinical characteristics of acute rupture of the chordae tendineae of the mitral valve in infants. A. Sex differences. B. Seasonal differences. C. Age distribution of the patients.

Figure 3. Surgical procedures and prognoses of the 95 patients.

Figure 4. Gross and histopathological findings of the mitral valves and ruptured chordae tendineae. A. Resected mitral leaflet of a patient (4-month-old male). B and C. Microphotographs of the valve and chordae tendineae of a 4-month-old female. The arrows indicate infiltrated mononuclear cells, and the arrowhead indicates a polymorphonuclear cell. D and E. Ruptured chordae tendineae of a 5-month-old female stained with hematoxylin and eosin (D) and Masson trichrome (E). The arrows indicate fibrin deposition at the ruptured chordae tendineae and the arrowheads indicate fibrous thickening with mononuclear cell infiltration at the
endocardium. **F.** Transverse sections of the chorda of the same patient (Masson trichrome). The arrow indicates a central core of dense collagen bundles and the arrowhead indicates fibrous thickening of the subendocardial tissue. **G.** Marked increase of fibrous thickening (arrow) between the endocardium and fibrous core (arrow). **H-J.** Microphotographs of chordae tendineae stained with hematoxylin and eosin (**H**) and toluidine blue (**I**), as well as immunohistochemistry with tenascin C antibodies (**J**) of a 6-month-old female. **K and L.** Immunohistochemistry with CD3 (**K**) and CD68 (**L**) antibodies at the rectangular area in **H.** The arrows in **K** indicate CD3-positive T-cells, and the arrows in **L** indicate CD68-positive macrophages. Scale in **A,** 1mm. Scale bars in **B, D-G,** 200 microns; **H-J,** 100 microns; **C, K and L,** 20 microns.

**Figure 5.** Kaplan-Meier survival estimates of time from diagnosis until artificial valve replacement. **A.** Artificial valve replacement-free survival in patients who developed chordal rupture in summer and those in other seasons. **B.** Artificial valve replacement-free survival in patients who developed 1-2 chordal rupture and those who developed 3-4.
Figure 2
Figure 3
Figure 5

A. Kaplan-Meier survival estimates

- Freedom from Artificial Valve Replacement
- Days
- Other Seasons
- Summer

B. Kaplan-Meier survival estimates

- Freedom from Artificial Valve Replacement
- Days
- Ruptured Chordae 1-2
- Ruptured Chordae 3-4
Acute Rupture of Chordae Tendineae of the Mitral Valve in Infants: A Nationwide Survey in Japan Exploring a New Syndrome

Isao Shiraishi, Kunihiro Nishimura, Heima Sakaguchi, Tadaaki Abe, Masataka Kitano, Kenichi Kurosaki, Hitoshi Kato, Koichi Sagawa, Hiroyuki Yamagishi, Toshio Nakanishi, Yoshihiko Ikeda, Takayuki Morisaki, Takashi Hoashi, Koji Kagisaki and Hajime Ichikawa

Circulation. published online July 25, 2014;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2014/07/25/CIRCULATIONAHA.114.008592