Summary of the 8th International Kawasaki Disease Symposium: Presentation of Selected Abstracts

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Abstract
The 8th International Kawasaki Disease Symposium (IKDS) brought together 279 health care professionals and scientists and 84 parents from 22 countries for a four-day symposium (February 17-20, 2005) in San Diego, California. Presentations covered diverse topics and the complete set of abstracts can be accessed at the American Heart Association website (http://www.americanheart.org/presenter.jhtml?identifier=3027303). In addition, two State of the Art Lectures and seven Invited Lectures were presented and a Parent Symposium and Nursing Symposium were embedded within the larger meeting. Despite progress in refining diagnostic procedures, new treatments, and a better understanding of disease pathology, Kawasaki disease (KD) remains an enigmatic condition of unknown etiology that continues to be the most common cause of acquired pediatric heart disease in many developed countries. The 9th IKDS will be held in Taiwan in 2008 and it is hoped that seeds of understanding that were planted at this conference will bear fruit by the time of the next international meeting.

NOTE: This conference summary is web-published only.
**Introduction**

This year marks the 37th anniversary of the publication of Dr. Kawasaki’s series of 50 Japanese patients and the 31st anniversary of the publication of this patient series in English (1, 2). Approximately 4,000 children are hospitalized each year in the U.S. with a diagnosis of Kawasaki disease (KD) according to estimates from hospital discharge databases (3). In Japan, over 8,000 new cases are diagnosed each year (4). Children who suffer the cardiac complications of KD have a life-time increased risk of myocardial ischemia, infarction, and sudden death (5). Thus, these children contribute to the burden of adult cardiovascular disease and have a large number of quality-adjusted life-years at risk for cardiovascular events.

Kawasaki disease provides an important model for understanding the pathophysiology of acute vasculitis and both the short- and long-term effects of inflammation on the myocardium and coronary arteries. Study of KD and its treatment are likely to yield important answers to general questions in cardiovascular health and disease that apply equally to pediatric and adult populations. These include 1) the influence of genetics on disease susceptibility, severity of inflammation, and response to therapy, 2) mechanisms of coronary artery damage following severe, acute inflammation, and 3) role of immune modulation in preventing coronary artery damage.

The first international Kawasaki Disease Symposium took place in 1984 in Hawaii and provided an important opportunity for interchange between American and Japanese investigators. Since that historic first meeting, the international symposium has been held every 3 years, alternating between Japan and Hawaii. The international community has always been well-represented at these meetings with attendees from all continents. A total of 168 abstracts were submitted to the meeting and the following is a summary of selected abstracts chosen by members of the 8th IKDS Organizing Committee for special comment. The abstract or poster (P) number is given in parentheses following the first author’s name so that readers can access the abstract at the website www.americanheart.org.

**Epidemiology**

Epidemiological descriptions of KD were reported from many countries throughout the world. In addition, with the formation of the International Consortium of Kawasaki Research Epidemiologists (ICKARE) and the creation of "Epi Night", physicians and scientists from around the globe were able to share their common interest in KD epidemiology.

Yosikazu Nakamura in his Invited Lecture at "Epi Night" reported on the epidemiology of KD in Japan. Data from the 17th nationwide survey, covering the years 2000-2001, revealed 16,952 new cases of KD, for an incidence rate of 145 cases/100,000 children less than 5 years of age. Japan now has a total of 186,069 reported cases of KD through the 17 surveys. Both the 17th nationwide survey and a report from a group who analyzed over 84,000 Japanese cases from 1987-2000 showed consistent seasonal variation in attack rates, with the highest number of cases reported in January and June and the fewest cases reported in October (# 2). This pronounced seasonality is consistent throughout the length of the Japan archipelago. Temporal clustering combined with marked seasonality suggest an environmental trigger acting over a large distance.

Similar to previous surveys, the 17th nationwide survey continues to show that in Japan the peak age of occurrence is in children under the age of 1 year, and KD is more common in boys than in girls. Overall, 1.3% of cases occurred in siblings, and there were recurrences in 3.6% of patients. Acute cardiac lesions were observed in 16.2% of the children (giant aneurysms were seen in 0.3%) whereas at 1 month after diagnosis only 5% of the patients had cardiac sequelae (giant aneurysms remained the same at 0.3%).
There were also reviews and reports from other Asian countries. Both Kritvikrom Durongpisitkul from Thailand (Epi Night presentation and P108) and HC Lue from Taiwan reviewed epidemiological reports of KD from many Asian countries other than Japan. Although the incidence rates varied widely, none of the countries had rates as high as Japan. Over 80% of the cases were in children younger than 5 years of age, and KD was more common in boys than in girls in all of the countries included. In contrast, a group in Indonesia who conducted a retrospective study in two hospitals in Jakarta found that over half of their cases were female (P63).

Y.W. Park and colleagues from the Republic of Korea (P79) reported on the epidemiology of KD in children 8 years of age and older. They found a significantly higher incidence of coronary artery abnormalities and aneurysms in older patients. Children 8 years and older comprised 1.3% of the 15,692 total cases from 1994 to 2002.

Ermias Belay from the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia USA gave an overview of the epidemiology of KD in the United States (Epi Night presentation). He discussed the CDC surveillance, which includes voluntary reporting of cases on a standardized case report form that is available at www.cdc.gov. In the CDC surveillance data, coronary artery aneurysms seem to be independently influenced by age, sex, and race. Surveillance and hospitalization data show seasonality, with more KD cases occurring during winter and spring. In the United States, a higher KD incidence has been consistently observed among younger children, boys, and children of Asian ancestry.

Additional US data were presented in a report by Robert Holman and colleagues on KD epidemiology in Hawaii (#1). This was a retrospective analysis of hospital discharge records of Hawaii residents with KD listed as a diagnosis from 1996-2001. The annual incidence for children <5 years of age averaged 45.2 per 100,000 children less than 5 years of age for the study period, and ranged from 38.7 per 100,000 children less than 5 years of age in 1996 to 56 per 100,000 children less than 5 years of age in 2001. Approximately 81% of patients were of Asian or Pacific Islander descent; 25% of children hospitalized with KD were Japanese-American. These children experienced the highest incidence of any race group -- 197.7 per 100,000 children less than 5 years of age. The next highest incidence rates per 100,000 children less than 5 years were for native Hawaiian (99.1), Chinese (81.3) and Filipino children (64.8). Caucasian children had the lowest incidence rate of 35.3/100,000 children less than 5 years of age. The KD incidence among Japanese-American children living in Hawaii appears to be higher than that reported for children in Japan (197.7 per 100,000 children less than 5 years of age in this study versus 134.2 per 100,000 children less than 5 year of age in Japan in 2000) and raises questions about either methodological differences in case finding or true differences in disease susceptibility between these two populations.

In San Diego County, California, an investigation by Annie Kao (#4) of space-time clustering and risk factors for KD showed that regions with a larger Asian population had higher incidence rates, and there was significant clustering of KD cases within three areas of the county. This significant clustering of cases within the space and time interval of 3 kilometers and 3-5 days supports the hypothesis of an infectious etiology.

Joyce Ching and colleagues presented a study of KD epidemiology in Canada from 2001 through 2003 (#3). They determined recent trends over a 36-month period in the incidence and clinical features of KD in Ontario (surveillance data) and the entire country (administrative data). They found that the incidence in Ontario appears to be increasing. It is currently 23.1/100,000 children less than 5 years of age, which is higher than surveys conducted in 1995-1997 and
1998-2000. Seasonal peaks continue, with the lowest numbers in late summer-early fall and the highest numbers in winter.

Finally, Eeva Salo from Finland gave an overview of KD in Nordic countries (Epi Night presentation). Incidence per 100,000 children less than 5 years of age was similar for the five countries included in her analysis -- 10.4 for Sweden, 7.2 for Norway, 11.7 for Denmark, 12.8 for Iceland and 11.5 for Finland. The mean age at onset is older than that reported for most Asian and North American countries (3.3 years for Sweden and 3.5 years for Finland). She also noted that mortality is higher in Sweden and Finland than in the other Nordic countries. This consistent difference in incidence rates between Nordic countries and North American countries raises the possibility of population statification that might influence genetic susceptibility in different Caucasian populations.

**Etiology and Pathogenesis**

Several presentations dealt with diverse methods to address the important problem of determining KD etiology. Frank Esper and colleagues (Late-breaking abstract #1) compared the prevalence of a newly described human coronavirus (HCoV-NH) in the upper respiratory tract of KD cases and controls, and identified viral RNA by RT-PCR in 8 of 11 children with KD (72.7%) but in only 1 of 22 controls (4.5%). They stated that none of three KD patients prospectively diagnosed since their initial study had HCoV-NH RNA detected in respiratory samples. It was suggested that HCoV-NH may be identical to HCoV-NL-63, a HCoV first reported in the Netherlands in 2004. Also presented were data from a multicenter group of KD investigators from the United States and the Netherlands, who examined respiratory samples from 42 acute KD patients in six laboratories and found HCoV-NL-63 RNA in only one patient. This multicenter group concluded that the presence of HCoV-NL-63 in the respiratory tract was not associated with acute KD.

Jon Graf and colleagues (Late-breaking abstract #2) took a different approach, screening a peptide phage display library with purified IgA from four patients with KD, to search for peptide sequences recognized by the KD antibodies. They were able to identify a nine amino acid consensus motif by this screening method, and are in the process of determining if KD sera, but not control sera, consistently recognize this nonapeptide.

Anne Rowley and colleagues (#7) reported results of a study to localize and further characterize the spheroidal bodies in acute KD ciliated bronchial epithelial cells that are detected by KD synthetic antibodies made from prevalent IgA sequences in acute KD arterial tissue. They used light microscopy stains and transmission electron microscopic analysis of bronchial epithelium from KD autopsy tissues to show that these spheroidal bodies represent intracytoplasmic inclusions, consistent with aggregates of viral proteins that may have associated nucleic acid.

Masaru Miura and colleagues (#14) used the same KD synthetic antibody in immunohistochemistry experiments on acute KD gastrointestinal tract (GI) and kidney tissues and detected antigen in two of seven acute KD patients but in none of seven control GI tissues. The antigen was localized to areas of severe GI pathology in the KD patients in deep tissues but not in mucosal epithelial cells. Antigen was not detected in the kidney from KD patients or controls.

Hiroko Shike and colleagues (P92) performed a culture and PCR study to determine whether adenoviruses or adeno-associated viruses are associated with acute KD, and found that neither group of viruses appeared to be infectious triggers for acute KD. Alexandra Freeman and colleagues (P85) inoculated acute KD throat and blood samples onto a variety of primary human cell cultures, in an attempt to find cells that might be susceptible to infection by the putative KD agent, with negative results. Other studies determined that KD was not associated
with abnormal immune responses to Epstein Barr virus infection (P70), and explored potential involvement of chlamydia in the pathogenesis of KD (P89).

Several presentations focused on potential animal models of KD. Karyl Barron and colleagues (#18) reported studies in which a chimpanzee experienced anaphylaxis following intravenous infusion of acute KD serum; other chimps were found to have positive immediate hypersensitivity skin tests to acute KD sera. A second chimp inoculated by aerosol with a throat swab eluate from an acute KD patient developed prolonged fever and other clinical signs similar to acute KD; investigation of the possible causative agent and additional chimpanzee experimental infections are ongoing. Joyce Hui-Yuen and colleagues (#20) reported that tumor necrosis factor (TNF-α) was necessary for the development of coronary arteritis in a Lactobacillus casei cell wall extract (LCCWE)-induced murine model of KD. Andrew Lau and colleagues examined the role of matrix metalloproteinase-9 (MMP-9) (P56) and elastin degradation (P57) in this model. Kathrin Michelson and colleagues (P52) determined that LCCWE activated cells via toll-like receptor (TLR) 2 and not TLR 4 in the same animal model. Other animal model studies including Candida albicans-cell wall induced arteritis in mice (P53) and an immune complex vasculitis of swine (P55) were also presented.

Kei Takahashi and colleagues (#17) examined autopsies of 7 children without coronary artery aneurysms who died of other causes after KD and concluded that non-aneurysmal coronary arteries were similar to matched control tissues and thus were unlikely to progress to stenosis. Several abstracts (P86, P87, P88, P104, #12, 15, 16) focused on the role of cytokines in the pathogenesis of KD, particularly the role of TNF-α produced by monocytes/macrophages (#12, 15) and cytokines acting on endothelial cells (#15, 16, P104). Higashi and colleagues reported that angiogenic activity in serum of acute KD patients with coronary artery disease was reduced (#8) and that a p38 mitogen-activated protein kinase inhibitor restored this activity in vitro. Two presentations (#9, 10) described a proteomic approach to identify unique protein patterns using two-dimensional gel electrophoresis and mass spectroscopy to analyze KD and control plasma. Other studies reported that Mac-1 expression was increased on neutrophils (P106), examined potential autoantigens in pathogenesis (P93, P105), determined the TLR repertoire in the peripheral blood (P91), found that CD8 T-cells were not making cytotoxic proteins in acute KD coronary artery aneurysms (P103), explored T-cell activation profiles (P102), performed DNA microarray analysis (P96, P99), examined plasma elastase levels (P90), and analyzed MMP levels (P62) in acute KD.

**Genetics and Gene Expression Studies**

Genetic variation and patterns of gene expression were lively areas of new research presented at the 8th IKDS with the presentation of 15 abstracts and two State-of-the-Art lectures. Presentations during the Epidemiology sessions clearly set the stage for investigations into the basis of the widely disparate frequencies of KD in different racial and ethnic groups. The role of genetic variation on susceptibility to KD was explored in several different populations. A presentation by Yoshihiro Onouchi (#22) described a genome-wide scan in 81 Japanese sibling pairs using microsatellite markers for multipoint linkage analysis that identified linkage to eight chromosomal regions. Of these, a region in 19q13 associated with three single nucleotide polymorphisms (SNPs) defined a linkage disequilibrium (LD) block of approximately 150 kb that was highly associated with KD. Sequence analysis revealed additional SNPs in the risk haplotype, but the risk gene was not disclosed. This powerful cohort of DNA samples will surely yield exciting information regarding the increased risk of KD among Japanese in the near future.

Additional presentations from Japan focused on case-control studies of selected polymorphisms. Takaomi Minami (P100) presented analysis of the V279F SNP in the platelet-activating factor acetylhydrolase (PAF-AH) gene in 76 Japanese KD patients and 112 healthy Japanese adults. Although no difference in allele frequency was detected between cases and
controls, a significantly higher frequency of the T allele and lower plasma levels of PAF-AH were found in the subset of KD patients who required additional doses of intravenous immunoglobulin (IVIG). Given the variability of IVIG treatment regimens in Japan, these data must be tested in additional cohorts with more uniform IVIG treatment. Toshiaki Jibiki (P98) presented an analysis of the relationship between eosinophil counts and the G-2518A SNP in the monocyte chemoattractant protein-1 (MCP-1) gene in 71 KD patients. Absolute eosinophil counts were higher in KD patients than in febrile controls and were significantly higher in the 59 KD patients carrying the G allele as compared to the 12 AA homozygotes. This suggests that genetic variation in MCP-1 may be linked to the T helper cell-2 (Th-2) phenotype and eosinophilia observed in KD patients.

Presentations from Korea explored a potential role for genetic variation in B-type natriuretic peptide (BNP) (P101) and angiotensin converting enzyme (P97) in KD susceptibility among Korean children. However, small sample size limited the power of these studies to detect a difference between cases and controls.

Studies in Caucasian populations included presentations from Australia, the Netherlands, and the U.S. David Burgener (#25) presented data suggesting a link between KD and a common major histocompatibility complex (MHC) Class I ancestral haplotype in Australian Caucasians. Maarten Biezeveld from the Netherlands (P94) reported a study of genetic variation in the mannose-binding lectin-2 (MBL2) gene that was differentially associated with development coronary artery lesions in patients younger and older than one year. Willemijn Breunis (#23) from the same Dutch group reported on genetic variation in the vascular endothelial growth factor (VEGF) gene and susceptibility to KD in Dutch children and found a difference in allele frequency for the C936T SNP between KD cases and controls. A poster presentation by Marina Dergun (P95) highlighted the familial occurrence of KD and described a series of sibling cases and complex pedigrees from North America with multiple affected members in different generations. Two presentations by Chisato Shimizu (#24 and #21) reported on a family-based analysis using the transmission disequilibrium test in trios of KD patients and their biologic parents from the U.S. A screen of 144 polymorphisms in 76 genes in 209 trios identified asymmetric transmission of alleles in 8 genes. Analysis of an independent cohort of 60 trios confirmed the asymmetric transmission of the C-589T allele in the promoter region of the Interleukin-4 (IL-4) gene. Because IL-4 is a key cytokine in stimulating the Th-2 response, these findings point to the importance of the Th-2 phenotype in KD children. In a second presentation based on the same U.S. cohort (#21), an important gene-gene interaction was described between haplotypes of the C-C chemokine receptor-5 (CCR5) and gene dosage of its most potent ligand, CCL3L1. The combination of reduced CCR5 expression associated with a 32-bp deletion in CCR5 (CCR5Δ32) and > 2 copies of the CCL3L1 gene was associated with protection from KD. The distribution of the CCR5Δ32 allele among different populations may contribute to the observed variability in KD incidence worldwide and may explain the low incidence of KD in Nordic countries described by Eeva Salo (see Epidemiology).

Gene expression studies analyzing transcript abundance in whole blood and cell subsets were the subject of four abstracts and one State of the Art Presentation. Saguna Verma (#26) presented data from eight KD patients whose whole blood RNA was analyzed using the Affymetrix chip. They found high expression of genes in the NF-κB pathway as well as increased expression of genes already implicated in KD pathogenesis including matrix metalloproteinases and cytokines. Jun Abe (#27) the gene expression profile of peripheral blood mononuclear cells and purified monocytes before and after IVIG treatment in acute KD patients. They concluded that IVIG induces a suppression of monocyte and macrophage activation. They focused on the S100 family of proteins and found that persistently elevated transcript and protein levels of S100A8 and A9 were associated with coronary artery aneurysm development.
Diagnosis and Treatment

The latest recommendations for diagnosis and treatment of KD by the American Heart Association (AHA) Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease were presented for international commentary. This statement, co-published in *Circulation* and *Pediatrics* in the fall of 2004, recommends treatment with high-dose IVIG for children with fever of four days duration and four of five classic clinical criteria, as well as for those with fewer clinical criteria in whom coronary abnormalities are noted by echocardiogram. In addition, a new algorithm incorporates laboratory tests and echocardiography to aid clinicians in deciding which children with fever for at least five days and fewer than four classic criteria (incomplete KD) should receive IVIG treatment.

Representatives from Australia, China, and Finland believed that the new algorithm would be useful in helping pediatricians to consider the diagnosis of KD. Those from Japan pointed out that Japanese pediatricians are highly sensitive to the diagnosis of KD and might find the proposed algorithm to be unnecessarily complicated. Sonobe and colleagues reported the prevalence of coronary artery abnormalities in incomplete KD in Japan. In the 17th nationwide survey, 16.3% of cases were incomplete. Compared to children with complete KD, those with incomplete clinical signs had a higher likelihood of coronary aneurysms (19.0% vs. 14.3%). For this reason, some Japanese experts believe that one should not wait until Day 5 of illness to treat incomplete KD with IVIG. Of note, however, IVIG treatment before Day 5 has not been associated with improved coronary artery outcomes.

Although IVIG has been shown in numerous randomized, controlled trials to reduce the incidence of coronary aneurysms, approximately 10 - 15% of children treated with IVIG will have persistent or recrudescent fever 48 hours after the infusion. These children are at higher risk for coronary artery aneurysms. Several presentations explored factors predicting IVIG resistance, including differences in host factors, such as immune gene polymorphisms and baseline sociodemographic and laboratory characteristics, variability in etiologic agents of KD, and variability in IVIG preparations. In addition, investigators reported studies of both primary and rescue therapy incorporating IVIG together with other anti-inflammatory agents.

In multiple studies, clinical factors predicting IVIG failure were reported to be similar to those predicting coronary aneurysms. In a case-control study using retrospective chart review, Kimiyasu Egami and colleagues (#32) compared pre-treatment characteristics of 82 patients who were IVIG-resistant, defined as those having persistent or recrudescent fever 48 hours after initial IVIG treatment, to those of 353 IVIG responders. Risk factors for IVIG resistance included male sex, age less than 4 months, cervical adenopathy, early treatment (Day 2-4 of illness), and higher baseline CRP, SGOT, SGPT, and total bilirubin, as well as lower albumin and serum sodium. In a large registry, Kritvikrom Durongpistikul and colleagues from Thailand (P108) found that low hemoglobin, high white blood cell count, and high erythrocyte sedimentation rate were significantly associated with IVIG resistance. Jun Furui and colleagues (P110) in Japan performed a matched case-control study using the database of the 17th national survey. The administration of additional IVIG treatment was used as a surrogate marker for resistance to the initial IVIG infusion. These investigators found that male gender, treatment within four days of illness onset, and absence of conjunctival injection were independent predictors in multivariate logistic regression of lack of response to initial IVIG. Given the finding of early IVIG treatment as a predictor of the need for IVIG retreatment, lively discussion ensued about the wisdom of this practice in the absence of demonstrable benefit.

Christine Bernal and colleagues (#31) presented intriguing work suggesting that the effect of IVIG on inhibition of the classical complement pathway-mediated lysis of sheep red blood cells is altered by pH. The investigators hypothesized that IVIG efficacy may be influenced by the pH of the commercial product, as well as by patient factors, such as blood volume and buffering capacity.
Tomio Kobayashi and colleagues (#30) examined the effect of steroid treatment on serum cytokines in a prospective, randomized trial of IVIG 1g/kg/day for two consecutive days versus IVIG together with prednisolone 2mg/kg/day, given intravenously in three daily doses until resolution of fever. Oral prednisolone was then gradually tapered until the CRP normalized. The total sample size was 40. Children treated with oral steroids had shorter duration of fever and duration to normalized CRP. In addition, steroid-treated patients had lower levels of Interleukin (IL)-2, IL-5, IL-8 and IL-10 within 24 hours of treatment.

Yoshinari Inoue and colleagues (P111) presented their experience in a prospective, randomized, multi-center clinical trial of IVIG alone (n = 77), 1g/kg/d for 2 days, versus IVIG plus corticosteroids (n = 76). The steroid group was treated with 2 mg/kg/day of prednisolone three times daily until the CRP level normalized, with a subsequent gradual taper. Those treated with steroids had significantly shorter duration of fever, faster resolution of CRP elevation, less need for IVIG retreatment, and lower incidence of coronary dilation at two weeks; they also showed a trend toward a lower incidence of coronary aneurysms at one month.

Masaru Miura and colleagues (#29) compared the efficacy of pulse steroids with additional immunoglobulin treatment of IVIG-resistant KD. In a series of 22 children with persistent or recrudescent fever after initial IVIG treatment (13%), 11 were treated with IVMP 30 mg/kg for three days plus heparin and 11 were treated with additional IVIG, 2 g/kg. In the IVMP group, 5 children had persistence of fever, and three required additional IVIG. In the IVIG group, 5 children had persistent fever, and 2 received IVMP. Compared to additional IVIG, IVMP induced faster but temporary resolution of fever, and was associated with more adverse effects of bradycardia, leukocytosis, and hyperglycemia. In audience discussion, some attendees advised an oral steroid taper to avoid rebound fever. Others stated that cost considerations favor steroid therapy.

Because TNF-α is a pro-inflammatory cytokine involved in KD pathogenesis, the role of TNF-α antagonists in treatment of refractory KD has been of particular interest. Infliximab is a chimeric IgG1 monoclonal antibody with human constant and murine variable regions that binds specifically to TNF-α and is currently approved for treatment of rheumatoid arthritis and Crohn’s disease in children. Gregory Kurio (#28) presented a retrospective series of 16 patients treated (median Day 22 of illness, range Day 8 - 53) with infliximab (5 mg/kg in 14, 10 mg/kg in 2) for refractory KD. All of these children had previously been treated with at least two infusions of high-dose IVIG and 8 had been treated with 1-5 infusions of pulse steroids (IV methylprednisolone, 30 mg/kg). One child with disseminated intravascular coagulation and coronary aneurysms prior to infliximab infusion had recurrence of fever and died 53 days after infliximab infusion. All of the other children defervesced within 24 hours and had reduction in CRP levels, without adverse effects. A prospective, Phase I study is currently in progress. Because reactivation of M. tuberculosis is a risk of infliximab treatment, this therapy should not be administered to patients who might have latent mycobacterial infection. This issue is further complicated by the fact that standard skin testing for tuberculosis may not be helpful because many patients with acute KD are anergic.

Cardiovascular Evaluation and Imaging

Although the meeting focused in great part on etiologic factors and pathogenetic mechanisms in KD, a number of interesting cardiology topics were also presented. Several reviewed current practices regarding coronary artery imaging and recent improvements using magnetic resonance imaging (MRI) and computed tomography (CT). Multislice spiral CT for imaging in older adolescents and young adults was reviewed in two presentations. Hiroshi Kanamaru (#35) reported this imaging technique to be particularly helpful in the diagnosis of late sequelae in patients with aneurysms. In this series, 96% of images were deemed adequate in these older
patients who are often difficult to image with ultrasound. Excellent agreement was found between CT and coronary angiography in the detection of stenoses and calcific changes in aneurysms. Raoul Arnold and colleagues (#36) compared multislice CT to gadolinium enhanced MRA in 10 patients (mean age 14 yrs.) and reported superior image quality with the CT system. Both studies strongly supported the use of multislice CT imaging in KD patients to reduce the need for invasive angiographic studies to diagnose and monitor coronary artery abnormalities. Shigeru Uemura (P148) reported the value of delayed-enhancement MRI to detect myocardial infarcts in 4 patients and compared results of MRI with thallium-SPECT results. In this small study, gadolinium-enhanced MRI was considered superior to SPECT protocols to detect myocardial infarcts, but larger numbers of KD patients will need to be studied.

Dajiji Takeuchi (P141) reported on ultrasound techniques to study physiologic changes during acute KD. They used tissue Doppler imaging to detect myocardial ischemia, suggesting microvascular impairment, and correlated these findings with markers such as BNP. These reports suggest a role for ultrasound in assessing the acute physiologic impact of KD even in the absence of coronary artery changes. These studies, plus another demonstrating elevated BNP levels in acute KD which normalized following IVIG administration (Chul Hee Woo, P142), emphasized the occurrence of microvascular changes in the myocardium in acute KD in patients with normal coronary arteries by echocardiography.

Subtle myocardial changes, even in the absence of prominent coronary artery abnormalities, were also demonstrated by Mathew Crystal in a study from Toronto (#P130) comparing electrocardiographic and echo findings in 176 KD patients, including a large number with incomplete KD. Only 4% had aneurysms evident on these studies, but ECG changes such as QT dispersion (a marker for arrhythmia risk) and echocardiographic changes in ventricular dimension (ventricular dilation) occurred much more frequently and persisted independent of coronary artery involvement.

This group of studies serves to remind those caring for KD patients that myocardial metabolic and microvascular changes occur with much greater frequency than observed coronary artery abnormalities. The long term consequences of these changes are yet to be clearly delineated, but data suggest that this is an important area for future study.

**Coronary Artery Interventions**

Three studies were presented regarding treatment for thrombotic coronary occlusion. Masahiro Ishii (#37) reviewed 22 patients who underwent percutaneous transluminal coronary revascularization (PTCR) for treatment of coronary thrombosis causing acute myocardial infarction. Twenty of the 22 procedures were initially successful. However, during the follow-up period of 5-20 years (median 13 years), 1 patient died with recurrent infarction 7 days post-PTCR, 2 other patients died suddenly at 10 and 13 years post-PTCR, and 11 required additional interventions. Only 8 of 20 (40%) remained event-free over the long-term. A case report by Giancarlo Piovaccari and colleagues (P156) described a 28-year-old male with acute coronary syndrome with thrombotic occlusion of an aneurysmal left coronary artery, who benefited from intracoronary injection of recombinant t-PA (20 mg). His past medical history suggested KD in childhood. Previous reports have demonstrated the efficacy of thrombolytic therapy administered intravenously, and that option should be tried at first. Another case report by Byung Won Yoo (P158), described a 6-year-old boy with a nearly total thrombotic occlusion of the left anterior descending artery with a proximal discrete stenosis. Two PTFE-covered stents (JOSTENT Graftmaster) were deployed to cover both the stenotic segment and the occlusive thrombus. Although a subsequent echocardiogram showed patency of the stented vessel, close observation for restenosis is indicated. When covered stents become available for pediatric clinical trials, this approach should be considered in selected patients.
There were three reports on catheter interventions targeting stenotic or calcific lesions. Motofumi Iemura (#50) tracked 24 stenotic lesions in 23 patients, who received a variety of catheter interventions, including balloon angioplasty (n=4), stent implantation (n=7), rotational ablation (PTCRA) (n=11) and combined PTCRA and stent implantation (n=2). The average age at intervention was 6.4 years (range: 1.5-10.5 years). Immediate success was noted in 22 of 24 lesions (92%). One patient underwent surgery immediately after stent implantation. Two of the 4 patients who received balloon angioplasty developed restenoses, one of them requiring surgery. Univariate and multivariate logistic regression analysis identified no link between outcome and five variables: age of onset, age at intervention, time from onset to intervention, calcification index and minimum lumen diameter. Takehiko Kuramochi and colleagues (P155) noted a high initial success rate and favorable long-term outcome when PTCRA was applied to calcific coronary artery lesions in a multi-institution, retrospective analysis. Forty-five calcific lesions were targeted with 100% initial success rate. The restenosis rate was 8.9% at a mean follow-up of 15.4 ± 4 months. A neo-aneurysm was noted in 1 case. Restenosis was related to burr size less than 2.38mm (p<0.05). In contrast, Motoki Takamura (P157) reported restenosis in 3 of 7 lesions subjected to PTCRA within 6 months requiring surgical intervention in one patient. The authors concluded that early restenosis was associated with burr size smaller than 2.5mm, long-segment stenosis and possibly a very long interval from onset of KD. These presentations underscore the need for close collaboration between pediatric and adult interventional cardiologists to ensure the safety and success of these interventions.

In the only paper on surgical results, Kimiyasu Egami (P161) reported on the mid-term results of arterial bypass grafts in 9 children. The mean age at the onset of disease was 2.6 years and the mean interval from onset to surgery was 9 years. Thus, most of the patients were older than 5 years at the time of surgery. Arterial grafts included the internal thoracic artery (n=7), gastroepiploic artery (n=5) and an arterial free graft (n=1). All arterial grafts were patent and all patients were asymptomatic, although the longest follow-up period was only 4 years. The authors could not address outcome in young children under 5 years of age because of small numbers. Multi-institutional studies will be needed to evaluate the outcomes, complications, and optimal therapeutic strategies (catheter versus surgical intervention) in this special group of KD patients.

**Anticoagulant and Antithrombotic Therapies**

Ei Ikegami and colleagues (P164) examined the relationship between shear stress and thrombus formation. They measured peak velocities within small, medium and large coronary artery aneurysms, computed shear stress (SS) and SS gradients from normal to aneurysmal segments, and compared these values to the incidence of thrombus. They found that reduced SS in the aneurysm and large SS gradient in giant aneurysms were associated with thrombus formation. This study lends support to the current empirical practice of anticoagulation targeting giant aneurysms. Experience with low-molecular weight heparin (LMWH) was presented by Amy Chesney (#41). Sixteen patients with coronary artery aneurysms were treated with LMWH. The drug was continued for a median duration of 1 year. Anti-factor Xa was measured at a median interval of every 23 days. Of the 182 levels obtained, 30% resulted in dosage change with 20% of levels below the therapeutic range. Only 1 patient developed non-occlusive coronary artery thrombosis. Nine minor bleeding episodes were noted in six patients. The authors concluded that LMWH may be a safe and effective alternative to warfarin therapy, although randomized, prospective trials are needed. In a study of patients with giant coronary artery aneurysms, Yoko Sugahara and colleagues (#43) retrospectively compared 19 patients treated with warfarin and aspirin with 41 patients treated with aspirin alone. The incidence of acute myocardial infarction was significantly lower in the group that received warfarin plus aspirin compared to the aspirin alone group (5.2% v. 29.2%). Sudden death occurred in seven patients on aspirin alone but in none treated with warfarin plus aspirin. This study supports the
current consensus that warfarin plus aspirin therapy should be used in children with giant aneurysms, although randomized trials have not been performed.

Kathy Hinoki and colleagues (P159) analyzed the effect of different antibiotics on INR in 28 patients receiving chronic warfarin therapy. The effect on INR varied by patient gender and antibiotic with both increases and decreases in INR noted. Erythromycin, cefuroxime, and clindamycin were associated with an increased INR while ampicillin, cephalaxin, and amoxicillin/clavulanic acid were associated with no change. Amoxicillin increased INR more frequently in females than in males. Griseofulvin and azithromycin were associated with a decrease in INR. In the light of this information, the authors advocate “proactive” warfarin dosing in anticipation of antibiotic therapy.

Platelet aggregation studies in 11 KD patients on long-term antiplatelet drugs were reported by Masato Takahashi (#42). Using both static and dynamic methods to assess platelet function, the authors discovered two cases of patient non-compliance and one case of apparent aspirin resistance and concluded that in vitro platelet studies may be useful in monitoring KD patients with aneurysms on long-term anti-platelet therapy.

Teiji Akagi (P162) presented three case reports of pregnant young women with large coronary artery aneurysms. All three were treated with aspirin until the middle of the 2nd trimester. In one woman, aspirin was replaced by dipyridamole. In the other two women, aspirin therapy was discontinued for the duration of the pregnancy. No bleeding or thrombotic complications were noted in the mothers or their fetuses. Etsuko Tsuda and colleagues from Suita, Japan (#40) reported 11 pregnancies in 9 KD patients with severe coronary artery abnormalities but no ischemia in their pre-pregnancy evaluation. Three women took aspirin during the pregnancy and one woman took nitrates. Ten neonates were delivered at term and were healthy. One infant was born at 23 weeks and suffered complications of extreme prematurity. The optimal management of pregnant women with coronary artery sequelae of KD has not been determined.

Kenji Suda and colleagues (P160) reported a 16-month-old patient with multiple giant aneurysms and near-total obstruction of all 3 major coronary arteries who was treated with intermittent heparin infusion in an attempt to stimulate angiogenic hepatic growth factor. A pre-treatment stress thallium scan showed perfusion defects in the apical and postero-lateral regions. The patient underwent infusion of heparin (100 IU/kg) twice daily for one month, followed by once weekly infusion for 2 months. A follow-up thallium study showed disappearance of the postero-lateral defect. Angiography 9 months later showed recanalization of the right coronary artery and an ejection fraction of 50%. Possible benefit of intermittent heparin infusion combined with exercise was reported at a previous KD Symposium. A large scale, prospective clinical trial may be warranted to test this therapy.

**Long-Term Outcomes**

Since the great majority of KD patients, both with and without coronary artery sequelae, are expected to be long-term survivors, long-term outcomes are of particular interest. Indeed, mortality has decreased, as reported by Mamoru Ayusawa and colleagues (#51) from analysis of the Japanese Nationwide Surveillance, from 0.113% for the 13th to 0.010% for the 17th survey. Cardiac causes of death were mainly attributable to acute complications, including myocardial infarction, myocarditis, valve dysfunction, and aneurysm rupture.

A pressing issue relates to the degree to which children who have had KD are at increased risk for accelerated atherosclerosis. This increased risk may be mediated by the severity of coronary artery involvement, the presence of ongoing inflammation and the spectrum of known and novel cardiovascular risk factors. Non-invasive assessments of vascular structure and function have been used as surrogate measures for vascular health. Brian McCrindle and colleagues from
Toronto, Canada (#38) reported a case-control study of cardiovascular risk factors, and noted that the 52 KD patients did not have abnormal endothelial function compared to normal control subjects, as assessed by brachial artery reactivity in response to reactive hyperemia. In KD patients, reduced brachial artery reactivity was not related to past or present coronary artery abnormalities and the majority of cardiovascular risk factors, except increased fasting triglyceride and glucose levels. Similarly, Seena Abraham and colleagues in New York (#39) noted no differences between KD patients and control subjects with respect to cardiovascular risk factors. There were also no differences in markers of inflammation, such as cystatin C or inflammatory cytokines and their receptors, and non-invasive assessment of carotid intima-media thickness and arterial stiffness. These two studies suggest that KD patients may not be at increased risk of atherosclerotic changes, at least in the systemic arteries assessed in these studies.

In contrast, studies from Japan suggest differently. Masahiro Ishii and colleagues from Kurume, Japan (#44) assessed coronary artery endothelial function in response to acetylcholine and isosorbide dinitrate during angiography, and noted endothelial dysfunction in those patients with persistent or regressed aneurysms, but not in six patients with normal angiograms during the acute phase of KD. Brachial artery reactivity suggested impaired endothelial function in 15 KD patients with aneurysms, which improved following intravenous administration of vitamin C and persisted with a period of oral administration. Yoshihide Mitani and colleagues (#45) found elevated levels of C-reactive protein, which were correlated with other inflammatory markers, in those KD patients with persistent coronary artery abnormalities. Ayumi Niboshi and colleagues (#47) noted increased urine 8-isoprostane in KD patients regardless of coronary artery involvement, indicative of ongoing oxidative stress. Urine nitrite and nitrate levels were abnormal only in the KD patients with coronary artery lesions. They also noted impaired brachial artery reactivity. Ryuji Fukazawa and colleagues from Tokyo (#49) examined coronary aneurysm tissues in three children undergoing giant aneurysm reduction surgery and bypass, and noted senescence-associated phenotypes of gene expression consistent with early atherosclerosis. The differences in results between the North American and Japanese studies are difficult to reconcile, although there may be important differences in genetic factors, diet, obesity, and other cardiovascular risk factors.

Health-related quality of life is an important long-term outcome for KD patients. Hiromi Muta and colleagues from Kurume, Japan (#48) had young adult patients (mean age 23 years) complete the SF36 questionnaire, and showed somewhat better health-related quality of life scores compared to Japanese normal subjects. Scores in various subdomains were also normal, and were not affected by the patients’ coronary artery status. It would appear that despite ongoing guardedness regarding long-term prognosis, even patients with major coronary sequelae are currently experiencing satisfactory long-term outcomes.

Acknowledgements
This symposium was sponsored by the American Heart Association Scientific Councils on Cardiovascular Disease in the Young, Clinical Cardiology, and Cardiovascular Radiology and Intervention and co-sponsored by the Kawasaki Disease Foundation and the Japan Kawasaki Disease Research Center. The meeting was also supported by grants from the National Institutes of Health, Office of Rare Diseases, National Heart, Lung, and Blood Institute, and the Centers for Disease Control and Prevention.
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