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# Risk Factors for Adverse Events During Cardiovascular Magnetic Resonance in Congenital Heart Disease

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## ABSTRACT

***Purpose*: To assess the incidence and severity of adverse events (AE) associated with cardiovascular magnetic resonance (CMR) in a large cohort of patients with congenital heart disease and to identify independent risk factors for their occurrence. *Methods*: AEs were prospectively recorded from October 2002 through December 2004 and graded by 3 independent observers for severity, preventability, and attributability. The rate of adverse events was analyzed for each candidate variable using Fisher's exact test and independent predictors were identified by multiple logistic regression analysis. *Results*: There were 22 AEs among 1334 CMR studies (1.6%); 14 (63.5%) minor, 7 (32%) moderate, and 1 (4.5%) major. General anesthesia (GA) was used in 274 studies (20.5%) with 12 AEs (4.4%, $p < 0.001$). There were 7 AEs (6.3%, $p = 0.001$) in 112 studies on hospitalized patients, 5 AEs (5.2%, $p = 0.018$) in 97 patients under 1 year of age, and 3 AEs (2.2%, $p = 0.479$) in 134 patients with functional single ventricle. The highest rate of AEs was noted in inpatients under GA (10.4%, $p < 0.001$); most were in the intensive care unit. Use of anesthesia (OR 3.91 [95% CI 1.46, 10.48] $p = 0.007$) and inpatient status (OR 3.56 [95% CI 1.16, 10.89], $p = 0.026$) were independent predictors of AEs. *Conclusions*: CMR in patients with congenital heart disease has a low rate of AEs. Use of GA and examinations on hospitalized patients are independent risk factors for AEs with the most acutely ill patients at highest risk.**

## INTRODUCTION

Cardiovascular magnetic resonance (CMR) is rapidly growing as an important diagnostic modality in patients with congenital heart disease (CHD). Numerous studies have shown its high accuracy in the diagnosis of a wide range of congenital cardiac anomalies (1–8). While the ability of CMR to diagnose complex cardiac lesions continues to expand, this noninvasive test is expected to be accomplished with minimal morbidity. However, patients with CHD often present with compromised hemodynamic and respiratory status and may be more vulnerable to adverse events (AEs).

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Although several studies have demonstrated the safety of sedation during MRI in a general pediatric population (9–13), the safety profile of CMR in patients with CHD has not been investigated in detail. Therefore, this study was undertaken to assess the incidence and severity of AEs associated with CMR in a large cohort of consecutive patients with CHD and to identify independent risk factors for their occurrence.

## METHODS

### *Subjects*

A clinical database of all AEs was maintained for all CMR examinations performed at our institution between October 1, 2002 and December 31, 2004. All examinations from this time period in which images were obtained were then included in this study. The institutional Committee on Clinical Investigations approved this investigation.

### *CMR*

All examinations were performed on a 1.5 T scanner (GE Medical Systems, Milwaukee, Wisconsin, USA) using previously published techniques (5, 14, 15). General anesthesia

with endotracheal intubation was provided by pediatric cardiac anesthesia specialists and was administered in those patients unable to comply with the examination using a previously published protocol (16). The anesthetic technique was determined according to pre-procedure clinical evaluation of cardiac function and preference of the anesthesiologist. Gadopentetate dimeglumine (Magnevist, Berlex Laboratories, Montville, NJ) 0.2–0.3 mmol/kg was injected via a peripheral intravenous catheter either by hand in patients weighing $< 10$ kg or by power injector in patients in whom magnetic resonance angiography was indicated. Exam duration generally ranged from 60 to 90 minutes. At the end of each exam, the patient was evaluated by an MRI technologist or radiology nurse for AEs.

## *Data collection*

The database was prospectively acquired, including demographic information and the following variables: referral diagnosis, use of anesthesia, hospitalization status (inpatient or outpatient) and occurrence of AEs. A cardiologist recorded any AE occurrence at the time of the examination. To ensure capture of all events, the database was compared with the institutional electronic records, and missing entries were updated. Patients who underwent anesthesia were classified using the American Society of Anesthesiologists (ASA) physical status score (17) as follows: class I: normal healthy patient; class II: mild systemic disease; class III: severe systemic disease limiting activity but no incapacitation; class IV: incapacitating systemic disease that is a constant threat to life; and class V: moribund patients not expected to live 24 hours with or without surgery.

## *Adverse events*

Three independent observers, including a cardiac imager, a cardiac intensive care specialist, and a cardiac anesthesiologist, retrospectively reviewed all AEs. The incidents were scored for severity level, preventability, and attributability to the procedure based on institutional criteria (Table 1). The observers were blinded to each other's grading. Median scores were used for data analysis.

## *Data analysis*

A commercially available statistical package was used for data analysis (STATA version 9.0; STATA Corp, College Station, TX). The rate of AEs was analyzed for each of the categorical candidate variables, including use of anesthesia, hospitalization status, age $\leq 1$ year, and functional single ventricle anatomy using Fisher's exact test for univariate analysis. Statistically significant variables were then tested in a multivariate model using multiple logistic regression to identify independent predictors of AEs. The group of patients undergoing anesthesia was analyzed by hospitalization status, using two-sample Wilcoxon rank-sum test to compare median ages, and Fisher's exact test

**Table 1.** Classification of adverse event severity, preventability, and attributability

| Level | Severity | Preventability | Attributability |
|---|---|---|---|
| 1 | None: No harm, no change in condition, may have required monitoring to assess for potential change in condition, no intervention indicated | Not preventable: Events where no obvious breach of standard professional behavior or technique occurred; necessary precautions were taken; no clearly known alteration in method of care exists to prevent the event | Not attributable: Events that clearly bear no relation to the medical procedure, including any and all involved medications or anesthesia |
| 2 | Minor: Transient change in condition, not life threatening, condition returns to baseline, required monitoring, required minor intervention such as holding a medication, obtaining lab test(s), application of heat or cold | Possibly preventable: Events where definite breach of standard professional behavior or technique was not identified but may have occurred; necessary precautions may not have been taken; event may have been preventable by modification of behavior, technique or care | Possibly attributable: Events where clear evidence of relation to the medical procedure are not present, but such relation cannot be clearly ruled out |
| 3 | Moderate: Transient change in condition, may be life threatening if not treated, condition returns to baseline, required monitoring, required intervention such as reversal agent, additional medication, or transfer to ICU | Preventable: Events where definite breach of standard professional behavior or technique was identified; necessary precautions were not taken; event was preventable by modification of behavior, technique, or care | Attributable: Events that clearly are related to the medical procedure or to related medications or anesthesia |
| 4 | Major: Change in condition, life threatening if not treated, change in condition may be permanent, may have required initial or readmit to hospital, may have required transfer to ICU, required monitoring, required major intervention such as invasive procedure, intubation, hemodynamic support, blood product transfusion | | |
| 5 | Catastrophic- Death | | |

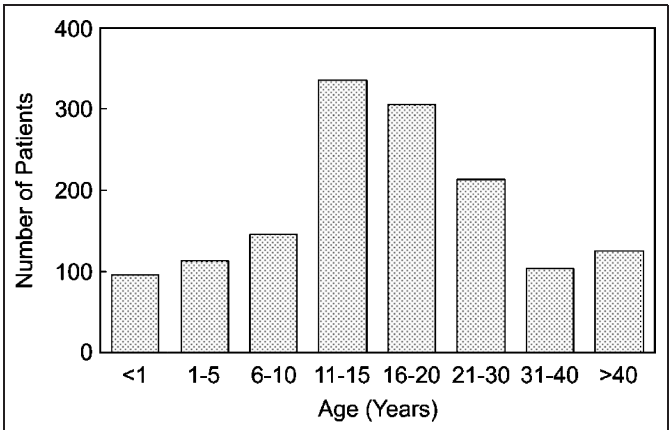


**Figure 1.** Histogram depicts the age distribution of patients included in the study.

for comparison of ordinal data. A two-tailed p value $<0.05$ was considered statistically significant.

## RESULTS

### *Subjects*

The study comprised 1334 CMR examinations on 1183 patients (57% male). Age ranged from 1 day to 75 years (median age 15 years) (Fig. 1). The primary referral diagnoses are listed in Table 2. General anesthesia was used in 274 examinations (20.5%). Inpatients accounted for 112 CMR studies, 44 of which were performed in patients referred from the intensive care unit (ICU) (39%). General anesthesia was used in 40 of the 44 studies on patients from the ICU (91%), and 32 of these patients were classified as ASA class IV. No other forms of sedation were used during the study period. None of the subjects in this study had a pacemaker generator or permanent leads.

### *Incidence, severity, and atributability of adverse events*

There were 22 AEs in 1334 CMR examinations (1.6%) (Table 3). The severity of the events was categorized as minor in 14 (63.5%), moderate in 7 (32%), and major in 1 (4.5%). All AEs were transient. AEs were determined to be possibly or definitely preventable in 3 cases (14%), with 19 (86%) classified as not preventable. AEs were definitely attributed to the procedure in 19 cases (86%), with 3 (14%) possibly related to the CMR examination.

### *Factors associated with adverse events*

The following patient- and technique-related variables were analyzed for their relationship with AEs (Fig. 2):

*Gadolinium contrast:* There were 9 contrast-related events in 1067 patients who received gadolinium contrast (0.84%). These events were predominantly minor (8/9) and were not associated with patient age, gender, admission status, or use of general anesthesia.

**Table 2.** Primary Referral Diagnoses in 1334 CMR Examinations

| Diagnosis | Number of Patients | Percent |
|---|---|---|
| Tetralogy of Fallot | 270 | 20.2 |
| Aorta | 198 | 14.8 |
| Coarctation | 116 | |
| Other | 82 | |
| Complex 2 Ventricle | 187 | 14.0 |
| TGA | 78 | |
| S/p arterial switch | 35 | |
| S/p atrial switch | 43 | |
| Single ventricle | 134 | 10.0 |
| Septal defects | 72 | 5.4 |
| ASD | 39 | |
| VSD | 33 | |
| Pulmonary veins-anomalous return or stenosis | 46 | 3.4 |
| Arrhythmogenic right ventricular cardiomyopathy | 41 | 3.1 |
| Pulmonary atresia with intact ventricular septum | 29 | 2.2 |
| Vascular anomalies (other than aorta) | 25 | 1.9 |
| Kawasaki disease | 24 | 1.8 |
| Congenital coronary anomaly | 22 | 1.6 |
| Cardiac tumor/mass | 22 | 1.6 |
| Vascular ring | 21 | 1.6 |
| Other | 243 | 18.2 |

TGA = transposition of the great arteries; ASD = atrial septal defect; VSD = ventricular septal defect

*General Anesthesia:* There were 12 AEs in 274 studies performed under general anesthesia (4.4%), compared to 0.9% in patients without anesthesia ($p < 0.001$). The incidence of AEs among inpatients receiving general anesthesia was significantly higher than in outpatients undergoing CMR under general anesthesia (10.4% v. 2.4%, $p = 0.011$). Compared to the outpatients with general anesthesia, the inpatient group was younger, more likely to have single ventricle physiology, and had higher ASA physical status scores (Table 4).

*Outpatient Status:* There were 10 AEs in 1015 outpatients studied without general anesthesia (1.0%), all of which were classified as minor. The incidence of AEs among outpatients studied with general anesthesia was not significantly higher than in those without (2.4% v. 1.0%, $p = 0.154$).

*Inpatient Status*: There were 7 AEs in 112 studies performed on hospitalized patients (6.3%), compared to 1.2% in outpatients ($p = 0.001$). The incidence of AEs among the 44 patients referred from the ICU was 9.2% ($p = 0.003$, compared with outpatients).

*Age*: There were 5 AEs in 97 studies performed on patients under the age of 1 year (5.2%), compared to 1.4% in patients over 1 year of age ($p = 0.018$).

*Single Ventricle Physiology*: There were 3 AEs in 134 studies performed on patients with functional single ventricle (2.2%), compared to 1.6% in patients with biventricular physiology ($p = 0.479$).

### *Multivariate analysis*

The factors found by univariate analysis to be associated with AEs were entered into a multiple logistic regression model. ICU

**Table 3.** Description of Adverse Events and Their Classification

| Adverse events | Severity | Preventability | Attributability |
|---|---|---|---|
| *Gadolinium-related* | | | |
| Emesis with gadolinium | Minor | No | Yes |
| Emesis with gadolinium | Minor | No | Yes |
| Emesis with gadolinium | Minor | No | Yes |
| Emesis with gadolinium | Minor | No | Yes |
| Nausea with gadolinium | Minor | No | Yes |
| Hives and dysphagia after gadolinium requiring diphenhydramine | Moderate | No | Yes |
| Warmth with gadolinium | Minor | No | Yes |
| Warmth and rash with gadolinium | Minor | No | Yes |
| Extravasation of gadolinium | Minor | Possible | Yes |
| *Anesthesia-hypotension* | | | |
| Hypotension during scanning requiring dopamine | Moderate | No | Yes |
| Hypotension during scanning requiring dopamine and admission to cardiac ICU | Moderate | No | Yes |
| Hypotension during induction requiring dopamine, epinephrine and fluid resuscitation | Major | No | Yes |
| Hypotension due to disruption of extension tubing carrying vasopressors | Minor | Yes | Yes |
| Hypotension and tachycardia with anesthesia induction | Minor | No | Yes |
| Hypotension and desaturation during scanning | Moderate | No | Possible |
| *Anesthesia-respiratory* | | | |
| Tachypnea and desaturation post-extubation, admitted to ward | Moderate | No | Yes |
| Bronchospasm requiring albuterol, atrovent and steroids | Minor | No | Yes |
| Hypoxia with breath holds | Minor | No | Yes |
| Pulmonary edema | Moderate | No | Possible |
| Pneumothorax in hospital post-MRI | Moderate | Possible | Yes |
| *Other medication-related* | | | |
| Rash following glycopyrrolate | None | No | Possible |
| Tachypnea, arm and back heaviness and anxiety with adenosine | Minor | No | Yes |

status was omitted due to its relationship to inpatient status. Use of anesthesia (OR 3.91 [95% CI 1.46, 10.48], p = 0.007) and inpatient status (OR 3.56 [95% CI 1.16, 10.89], p = 0.026) were independent predictors of adverse event in this cohort, while age under 1 year was not (OR 0.70 [95% CI 0.18, 2.66], p = 0.602).

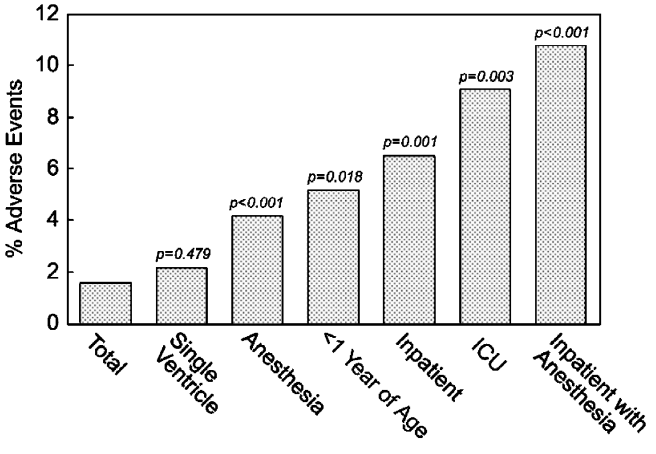


**Figure 2.** Histogram depicts the rate of adverse events by each variable tested. P values for ICU and Inpatient with Anesthesia are in comparison with outpatients. ICU is a subgroup of Inpatient.

## DISCUSSION

The results of this study demonstrate that CMR in patients with CHD is safe with a low rate (1.6%) of AEs. The use of general anesthesia and studies performed on hospitalized patients were associated with the occurrence of AEs. The majority of the events were minor in severity, and all were transient.

### *Patients at risk of adverse events*

The patients at highest risk of AEs were those who were hospitalized at the time of the examination and required general

**Table 4.** Comparison between Outpatient and Inpatient CMR Examinations under General Anesthesia

| | Inpatient (N = 67) | Outpatient (N = 207) | p value |
|---|---|---|---|
| Median age (years) (range) | 0.3 (0.1–17) | 4.1 (0.1–57.9) | <0.001* |
| Age ≤1 month | 23 (43%) | 2 (1%) | <0.001 |
| Age ≤1 year | 52 (78%) | 44 (21%) | <0.001 |
| Gender (% male) | 39 (58%) | 95 (46%) | 0.092 |
| ASA class (%) | | | <0.001 |
| II | 2 (3%) | 53 (26%) | |
| III | 30 (45%) | 146 (70%) | |
| IV | 35 (52%) | 8 (4%) | |
| Functional single ventricle (%) | 23 (34%) | 31 (15%) | 0.001 |
| Referral from the ICU (%) | 40 (60%) | | |

*Two-sample Wilcoxon rank-sum test. All other P values by Fisher's exact test.

anesthesia. This group of 67 patients, which accounted for only 5% of all studies, was responsible for 7/22 (32%) of all AEs, and for 5/8 (63%) of the AEs rated moderate or major in severity. Importantly, this group represents the most acutely ill patients in this study; most (40/67, 60%) were in the intensive care unit at the time of CMR.

Although the clinical role of CMR in infants with CHD has been reported (18), the incidence and severity of AEs in this group of patients have not been previously evaluated in detail. The findings of this study highlight the importance of carefully weighing the risks and benefits of CMR in patients with severely compromised cardio-respiratory status. Echocardiography at the bedside is well established as the primary test for a detailed cardiac imaging evaluation and carries little risk. The need for additional diagnostic evaluation typically arises when clinical questions cannot be satisfactorily addressed by this modality. In these circumstances, the risks and benefits of CMR are usually considered in comparison with the risks of a delay in diagnosis, as well as the risks of cardiac catheterization and computed tomography, neither of which is risk-free. Cardiac catheterization, in particular, has been shown to be higher risk in patients with cardio-respiratory compromise. In a study of 4,952 pediatric catheterizations, Vitiello et al (19) showed that all 7 deaths in their study occurred in critically ill children, most of whom were neonates.

### *Use of anesthesia*

General anesthesia has been used at our institution for CMR in most children who are unable to cooperate (usually younger than 6 to 8 years old) (16, 18). This has been the preferred approach for the cardiac anesthesiologists at our center, due to the duration of the CMR procedure, the need to protect the patient's airway, and the desire to avoid possible respiratory depression and hemodynamic changes associated with continuous intravenous sedation. In addition, this approach allows for breath holding during the examination, providing optimal image quality for 3-dimensional MR angiography, cine and black blood sequences.

The ability to perform these procedures safely has been published and is confirmed by the findings of this study, whose patients do not overlap those in the study by Odegard et al. (16). Other centers use different strategies for sedation of patients who are unable to cooperate with a CMR examination. In a general pediatric population presenting for MRI, Beekman et al (9) showed that rectal thiopental achieved adequate sedation in 95% of their patients with 2.5% incidence of minor adverse events. Although this and other sedation regimens are commonly employed in clinically stable outpatient diagnostic imaging procedures, less information is available on their safety and efficacy in high-risk populations, such as those in our study. Vade et al (20) examined the safety of chloral hydrate sedation in a general pediatric population for CT or MRI examinations but excluded patients who were ASA class III or higher. Of the 410 patients included in that study, 2 patients developed hypoxia with oxygen saturation <90%. In retrospect, both of those patients were found to actually be ASA class III, including an infant with single ventricle heart disease. In addition, Sanborn et al (21) studied adverse respiratory and cardiovascular events during sedation of pediatric patients referred for CT or MR and found that 20 of the 70 patients who had adverse respiratory events (out of 16,467 sedations) had a history of serious respiratory illness. Although not studied directly, it is likely that the high-risk group from the current study, consisting of anesthetized inpatients, 97% of whom were ASA class III or greater, would likewise be at high risk for sedation-related complications. In the absence of a randomized clinical trial comparing sedation with general anesthesia in patients with CHD, the safety profile of one strategy versus the other remains speculative.

### *Limitations*

This study protocol did not include a follow-up telephone call to the patients after their CMR. Therefore, it is possible that minor, delayed events occurring after patient discharge were not captured. However, given that most patients referred for CMR at our center are followed by local cardiologists, it is likely that any significant delayed events, resulting in visits to the Emergency Department or in readmission to the hospital, would have come to our attention. In addition, some gadolinium-related events such as nausea or sensation of warmth were subjective in nature and, therefore, were likely under-reported in patients who received general anesthesia.

## CONCLUSIONS

CMR is a safe diagnostic modality in patients with CHD, with a low rate of AEs, most of which are minor and transient. For patients at highest risk of adverse event, who are hospitalized and require anesthesia for the examination, a careful analysis of the risks and benefits of CMR and its alternatives is warranted.

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