Pamela K. Woodard, MD
Eric Chou, MD
Jerome L. Fleg, MD
Quynh A. Truong, MD, MPH
Maros Ferencik, MD, PhD
Udo Hoffmann, MD, MPH

*Cardiac MR PET CT Program
Division of Cardiac MR/PET/CT
Massachusetts General Hospital
165 Cambridge Street, Suite 400
Boston, Massachusetts 02114
E-mail: sjanjua@partners.org

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High Platelet Reactivity and Intrastent Thrombi Assessed by OCT After DES

High platelet reactivity (HPR) on clopidogrel may be related to stent thrombosis after drug-eluting stent (DES) implantation (1). To investigate the relationship between HPR and intrastent thrombi following DES implantation, 202 lesions treated with DES from 109 patients were studied. Coronary angiography and optical coherence tomography (OCT) examination were performed as parts of routine follow-up examination at our institution except for the presence of renal dysfunction or congestive heart failure. OCT imaging and platelet function test were performed at 6 to 9 months (median 202 days). Dual antiplatelet therapy with aspirin and clopidogrel was started before stent implantation and continued for at least 1 year. In patients with acute coronary syndrome who underwent emergent coronary intervention, a loading dose of clopidogrel (300 mg) was started on arrival to the emergency department and a maintenance dose (75 mg) was continued thereafter. In patients with stable angina pectoris who underwent elective coronary intervention, a maintenance dose (75 mg) of clopidogrel was started at least 2 weeks before intervention and continued thereafter. Neither prasugrel nor ticagrelor was used because they were not commercially available at the time of this study.

By OCT, intrastent thrombus was defined as a mass (≥100 μm) with an irregular surface attached to the vessel wall or stent struts that protrude into the lumen (2). Stent and lumen areas were measured, and neointimal area was calculated as stent area minus the lumen area at the minimal stent area site. Blood samples for platelet function tests were obtained during cardiac catheterization and measured within 3 h after OCT imaging using the VerifyNow system (Accumetrics, San Diego, California). The platelet reactivity to adenosine diphosphate was quantified as $P2Y_{12}$ reaction unit (PRU). HPR was defined as PRU ≥230 rather than ≥208, because our study patients were an East-Asian population who have different thrombogenicity from Western populations and thus have different cutoff values (1–3). Data are presented as mean ± SD for continuous variables and as frequency (%) for categorical variables. Student *t* test was used to compare continuous variables and the chi-square test or Fisher exact test was used to compare categorical variables. For lesion-based comparison, no adjustments were made for evaluation of multiple lesions within individuals. Statistical analysis was performed with the SPSS version 22.0 for Windows (SPSS Inc., Chicago, Illinois), and $p < 0.05$ was considered statistically significant.

HPR was documented in 35 patients (32%). Angiography and OCT were performed at 292 days (interquartile range [IQR]: 272 to 545) in patients with HPR and 296 days (IQR: 271 to 595) in patients without HPR ($p = 0.876$). The time from the last dose of clopidogrel to VerifyNow testing was similar between the 2 groups (249 ± 150 min vs. 191 ± 134 min). **Table 1** summarizes patients and lesion characteristics.

TABLE 1 Patient and Lesion Characteristics

Patient-Based Analysis	HPR(+) (n = 35)	HPR(−) (n = 74)	p Value
Median follow-up time, days	292	296	0.870
Age, yrs	71 ± 9	67 ± 10	0.041
Male	22 (63)	60 (81)	0.040
Diabetes mellitus	21 (60)	32 (43)	0.102
Hyperlipidemia	23 (66)	52 (70)	0.632
Hypertension	30 (86)	52 (70)	0.081
Smoking	6 (17)	19 (26)	0.322
Hemodialysis	2 (6)	1 (1)	0.194
Family history	5 (14)	10 (14)	0.913
Acute coronary syndrome	20 (57)	29 (39)	0.079
Myocardial infarction	12 (34)	30 (41)	0.531
Coronary artery bypass surgery	2 (6)	5 (7)	0.836
$P2Y_{12}$ reaction unit	274 ± 31	162 ± 51	0.004
Medications			
ACEI/ARB	26 (74)	45 (61)	0.168
Statin	22 (63)	55 (74)	0.220
Antidiabetics	16 (46)	20 (27)	0.053
Beta-blockers	13 (37)	23 (31)	0.530
Calcium-channel blockers	19 (54)	25 (34)	0.042
Proton pump inhibitor	20 (57)	33 (45)	0.221
Warfarin	2 (6)	3 (4)	0.699
Aspirin	35 (100)	74 (100)	–
Clopidogrel	35 (100)	74 (100)	–
Lesion-Based Analysis	**(n = 65)**	**(n = 137)**	
Target lesion			
LAD/LCX/RCA/SVG	33/8/22/2	70/25/40/2	0.605
Stent			0.105
Sirolimus-eluting stent	1 (2)	6 (4)	
Paclitaxel-eluting stent	2 (3)	1 (1)	
Zotarolimus-eluting stent	13 (20)	8 (6)	
Everolimus-eluting stent	39 (60)	93 (68)	
Biolimus-eluting stent	10 (15)	29 (21)	
Procedure and QCA			
Procedure time, min	123 ± 49	124 ± 48	0.762
Pre-dilation/direct stenting	37/28	96/41	0.066
Maximal inflation pressure, atm	17 ± 2.6	17 ± 3.3	0.624
Minimal stent diameter, mm	2.0 ± 0.52	2.0 ± 0.42	0.437
Stent length, mm	22 ± 7.3	23 ± 7.1	0.434
Diameter stenosis, %	20 ± 24	17 ± 18	0.387
OCT			
Lumen area, mm^2	4.1 ± 1.9	4.3 ± 1.9	0.523
Stent area, mm^2	5.7 ± 2.0	5.8 ± 2.0	0.675
Neointimal area, mm^2	1.5 ± 1.1	1.5 ± 1.1	0.740
Incomplete stent apposition	16 (25)	35 (26)	0.887
Thrombus	13 (20)	5 (3.6)	0.001
White/red thrombus	12/1	5/0	

Values are n, mean ± SD, or n (%). **Dashes** indicate not available because both group were 100% and no statistical comparison could be done.

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin-receptor blockers; HPR = high platelet reactivity; LAD = left anterior descending; LCX = left circumflex; OCT = optical coherence tomography; QCA = quantitative coronary angiography; RCA = right coronary artery; SVG = saphenous vein graft.

Intrastent thrombi were observed in 13 of 65 lesions (20%) in patients with HPR and in only 5 of the 137 lesions (3%) in patients without HPR ($p < 0.01$). By patient-based analysis, intrastent thrombi were detected in 10 of 35 patients (29%) with HPR and in only 4 of 74 patients (5%) without HPR ($p < 0.01$).

The principal findings of this study were that HPR was present in 35% of the patients treated with DES and intrastent thrombi were more frequently detected by OCT in patients with than those without HPR. Results of our present study may explain higher incidence of stent thrombosis after DES in patients with HPR despite continuous dual antiplatelet therapy (1). Because of small sample size and a retrospective study design, direct connection between intrastent thrombi and stent thrombosis could not be elucidated. Clinical impact of intrastent thrombi needs to be investigated further. Because we excluded patients who are not suitable for OCT imaging, possible selection bias may be present. Because of small numbers of each DES, comparisons among different types of DES were not performed. CYP2C19 genotypes were not studied in this study. Therefore, the direct relationship between genotypes and intrastent thrombi is unknown.

In the present retrospective study, a higher incidence of intrastent thrombus was found during follow-up in asymptomatic patients with HPR on clopidogrel. Further study is required to determine the clinical implications of this finding, including whether a change in antiplatelet therapy is warranted.

Kenzo Fukuhara, MD
Hiroyuki Okura, MD*
Teruyoshi Kume, MD
Ryotaro Yamada, MD
Yoji Neishi, MD
Shiro Uemura, MD
Kiyoshi Yoshida, MD

*First Department of Internal Medicine
Nara Medical University
840 Shijo, Kashihara
Nara 634-8522, Japan
E-mail: hokura@fides.dti.ne.jp

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Echocardiographic Predictors of Mortality in Adults With a Fontan Circulation

Adults with univentricular physiology repaired with a Fontan-type procedure are at increased risk of premature death. We investigated echocardiographic indexes that are predictive of mortality in this setting because the prognostic utility of such imaging is not well characterized.

Adults who had undergone a Fontan procedure and had been seen at our institution since 2005 were screened. Exclusion criteria were Kawashima repair, pregnancy, ventricular outflow gradient >2.0 m/s, supraventricular arrhythmia during transthoracic echocardiogram, or paced ventricular rhythm. Follow-up continued until time of death, total cavopulmonary connection (TCPC) conversion, or most recent review.

Standard 2-dimensional and Doppler echocardiographic assessments were performed. In addition, systolic duration was measured from the onset to the end of atrioventricular (AV) valve regurgitation. Diastolic duration was measured from the end of AV valve regurgitation to the onset of the subsequent AV valve regurgitation signal. The AV systolic to diastolic duration ratio (S/D duration ratio) was then calculated.

One hundred twenty-eight patients (64 men; median age 25 [interquartile range (IQR): 20 to 30] years; 107 [84%] with dominant left ventricle) were included. New York Heart Association functional class was I/II in 120 patients (94%) and III/IV in 8 (6%). Forty-eight had atriopulmonary connection (APC), and 80 had TCPC, of whom 16 had undergone an APC to TCPC conversion as an adult. Median follow-up was 4.2 years (IQR: 1.5 to 6.6 years). Overall, 75 patients (59%) had good systolic function by qualitative assessment. Thirty-eight patients (30%) had mild systolic impairment, 8 (6%) had moderate systolic impairment, and 7 (5%) had severe systolic impairment. One hundred eight patients (84%) had no AV valve regurgitation or mild AV valve regurgitation, and 20 (16%) had moderate to severe AV valve regurgitation.

Twelve patients (9%) died during follow-up (age 37 [IQR: 29 to 45] years). Seven of those had APC, 3 had TCPC, and 2 had TCPC conversion. Eight deaths were due to heart failure, 2 were sudden, and 2 were due to liver failure. The results of univariable Cox regression analysis are shown in **Figure 1A**. When accounting for Bonferroni correction (significance $p < 0.003$), only functional class and S/D duration ratio remained significant predictors of death. Kaplan-Meier survival analysis is shown in **Figure 1B**. We performed post hoc analysis to assess whether atrioventricular S/D duration ratio correlated with other transthoracic echocardiogram measures of ventricular function. A significant correlation existed with subjective grade of ventricular function ($R = 0.32$; $p = 0.006$), fractional area change ($R = -0.25$; $p = 0.04$), and E/A ratio ($R = -0.23$; $p = 0.009$). Atrioventricular S/D duration ratio did not correlate with age ($R = -0.04$; $p = 0.7$) but had a strong correlation with heart rate ($R = 0.58$; $p < 0.0001$). On univariable analysis, S/D duration ratio corrected for heart rate remained a strong predictor (hazard ratio: 7.5; $p < 0.0001$), whereas heart rate was associated with a lesser hazard ratio (1.1; $p = 0.02$).

This study suggests that S/D duration ratio is an especially important prognostic marker in Fontan patients. Assessment of single-ventricular function with echocardiography, the mainstay of cardiac imaging in Fontan-palliated adults, is challenging. S/D duration ratio reflects global ventricular function and can be measured simply and consistently using continuous-wave Doppler assessment of the AV valve. This may be of particular significance in Fontan patients but has only been explored previously in a pediatric group with hypoplastic left heart syndrome at various stages of Norwood palliation (1), and tissue Doppler-derived S/D duration ratio has been reported not to correlate with magnetic resonance imaging-derived measures of systolic function in that setting (2). Tissue Doppler-derived indices that reflect motion in one wall might be less useful (because of dyssynchronous contraction) than continuous-wave Doppler-derived measurement in the setting of complex single-ventricle hearts.

Data investigating the relation between echocardiography and clinical outcomes in the Fontan circulation are scarce. Poor ventricular function and degree of AV valve regurgitation have been retrospectively associated with risk of death (3). In Fontan patients with protein-losing enteropathy, deceleration time <120 ms predicted mortality (4). Ghelani