in 38,602 patients (nonshunt group). An intracardiac shunt was identified in 418 patients in the perflutren group (40 detected at rest only, 128 detected following Valsalva maneuver only, 84 detected with both; 166 unknown). Patients with left-to-right shunts only (n = 63; detected by color Doppler) were excluded from analysis. No primary adverse events occurred in the shunt group; 1 occurred in the nonshunt group (p = 0.99) (Table 1). One secondary adverse event occurred in the shunt group, and 34 in the nonshunt group (p = 0.31). All events occurred in studies using Definity (vs. Optison; p = 0.03). Right heart contrast studies were performed in 3,661 patients (1,432 with perflutren, 2,229 without perflutren); intracardiac shunts were diagnosed in 839 patients (23%).

The International Contrast Ultrasound Society recently raised concerns about the current contraindication of perflutren use in patients with known/suspected intracardiac shunts, recommending that this contraindication be removed to improve patient care and reduce unnecessary downstream testing (1). Agitated saline, a first-generation echocardiographic contrast agent (hand-agitated, with tremendous heterogeneity in bubble size) has been widely used during transthoracic and transesophageal echocardiograms to detect intracardiac shunts, without regulatory oversight (1). However, the greater diffusibility of air in the circulation, and lack of CARPA reactions to agitated saline, probably do not allow for a direct comparison with perflutren. The current observational study is the first to assess the use of perflutren in patients with intracardiac shunts, and it demonstrates that the overall incidence of adverse events was low in patients receiving perflutren. Importantly, perflutren use in patients with these shunts (without cyanotic congenital heart disease) was not associated with significant adverse neurological and/or systemic embolic events compared with use in patients without diagnosed intracardiac shunts. Similarly, perflutren use was not associated with any significant difference in secondary adverse events (CARPA reaction) in patients with intracardiac shunts. Of note, all CARPA reactions in our cohort occurred with use of Definity and were consistent with previously published data from our laboratory (2).

Study limitations include potential underestimation of adverse event incidence due to incomplete registry ascertainment, occurrence more than 30 min after perflutren administration, or occurrence in sedated or unconscious patients. Also, relatively modest numbers of intracardiac shunts were noted in the perflutren group, which was attributable to potential selection bias and possibly the impact of the Food and Drug Administration's 2001 contraindication of perflutren use in patients with intracardiac shunts.

The current proscription of perflutren is logically untenable in clinical practice, as it is based on a "don't ask, don't tell" paradigm for shunt detection in patients who are potential candidates for receiving perflutren. Our data indicate that the current proscription of perflutren use in patients with intracardiac shunts should be rescinded.

Table 1. Primary and Secondary Adverse Events With Perflutren-Based Echocardiographic Contrast Agent Use in Patients With and Without Right-to-Left, Bidirectional, or Transient Right-to-Left Intracardiac Shunts

	Intracardiac Shunt			
	Yes	No	Total	p Value
Perflutren-based ECA use	418	38,602	39,020	
Primary adverse events	0	1	1	0.99
Transient ischemic attack	0	1 (0.0026)		
Secondary adverse events	1	34	35	0.31
Angioedema	0	1 (0.0026)		
Back pain	1 (0.24)	24 (0.0622)		
Bronchospasm	0	1 (0.0026)		
Hypotension	0	2 (0.0052)		
Hypoxemia	0	1 (0.0026)		
Urticaria	0	4 (0.0104)		
Vasovagal reaction	0	1 (0.0026)		
Other events	0	1	1	
Seizure	0	1 (0.0026)		

Values are n or n (%).
ECA = echocardiographic contrast agent.

Ankur Kalra, MD, Gautam R. Shroff, MD, Darryl Erlien, MS, David T. Gilbertson, PhD, Charles A. Herzog, MD*

*Chronic Disease Research Group, Minneapolis Medical Research Foundation, 914 South 8th Street, Suite S4.100, Minneapolis, Minnesota 55404. *E-mail:* *cherzog@cdrg.org*

http://dx.doi.org/10.1016/j.jcmg.2013.11.003

Please note: Dr. Herzog owns equity interest in General Electric. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Parker JM, Weller MW, Feinstein LM, et al. Safety of ultrasound contrast agents in patients with known or suspected cardiac shunts. Am J Cardiol 2013;112:1039–45.
2. Herzog CA. Incidence of adverse events associated with use of perflutren contrast agents for echocardiography. JAMA 2008;299:2023–5.

LV Noncompaction in Ebstein's Anomaly in Infants and Outcomes

Left ventricular noncompaction (LVNC) is a distinct primary myocardial disease characterized by abnormally prominent trabeculations in the ventricular myocardium, and is reported to coexist with congenital heart diseases like Ebstein's anomaly (EA) and others (1). The clinical course of LVNC with EA is unknown in the pediatric literature. We report a pediatric cohort of LVNC and EA, with emphasis on the natural course and the outcome.

We conducted a retrospective search of our institutional database from 2002 to 2007 for patients with EA and LVNC. This cohort was divided into 2 groups: group 1, patients with EA and LVNC; and group 2, patients with EA alone. We reviewed patients' medical records and collected information on the age at diagnosis, clinical presentation, electrocardiographic features, echocardiographic severity of the LVNC based on the extent of

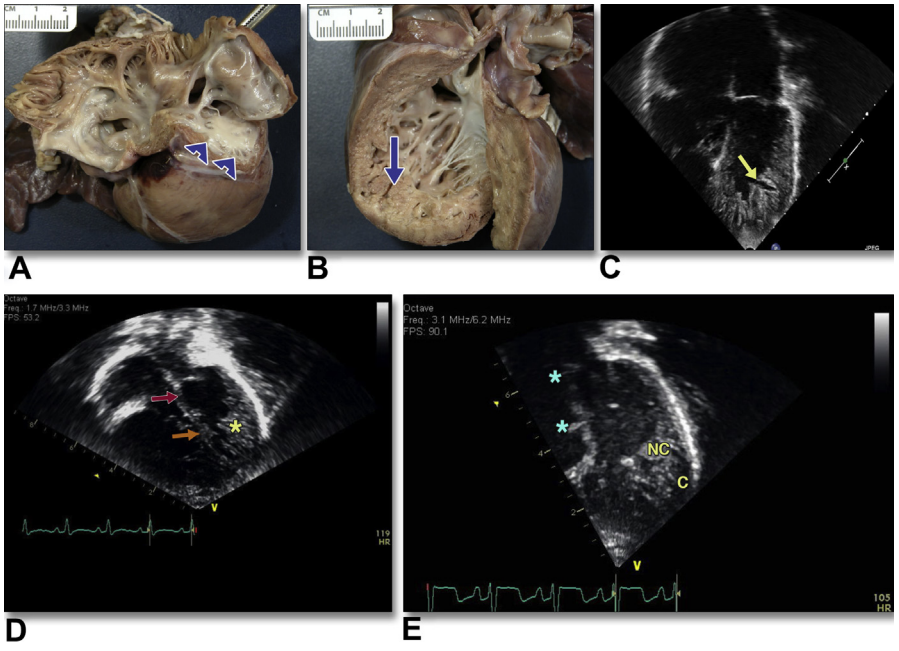

Figure 1. Correlation of Pathologic Findings and 2D Echocardiography in Ebstein's Anomaly and LVNC

(A) Autopsy specimen of a neonate with Ebstein's anomaly, with right atrium opened to show the small right ventricle, plastered septal leaflet **(arrowheads),** and **(B)** the dense trabeculations with recesses in the left ventricle (LV) **(arrow)**. **(C)** Echocardiogram in the apical 4-chamber view, showing the trabeculations in the LV **(arrow)**. **(D)** Ebstein's anomaly **(arrows)** with prominent trabeculations in the lateral wall of the LV **(*)**, and **(E)** showing the displaced septal leaflet of the tricuspid valve **(**)**. 2D = 2-dimensional; C = compacted myocardium; LVNC = left ventricular noncompaction; NC = noncompacted myocardium with trabeculations.

distribution of abnormal myocardial trabeculations (the extent of the distribution of abnormal left ventricular [LV] myocardial trabeculations to the lateral wall, apex, and the ventricular septum were labeled as segments 1, 2, and 3, respectively), LV end-diastolic dimension indexed to the body surface area (with z scores), ejection fraction (by Simpson biplane method) at initial diagnosis and at latest follow-up, management (medical therapy, catheter interventions, and surgeries), length of follow-up (in months), and the outcome (alive or dead). All echocardiograms were reviewed for LVNC, as defined by the standard echocardiographic criteria, by 2 independent observers blinded to clinical data.

Sixty-one patients were identified; 10 patients (16%) showed EA and LVNC (group 1) (Fig. 1). The remaining 51 patients (84%) showed EA alone (group 2). Nine of 10 patients (90%) in group 1 were diagnosed at birth with a suspicion of LVNC on the fetal echocardiogram. In addition, 4 of 10 patients (40%) showed cyanosis at birth, with right-to-left shunting across the patent foramen ovale. All patients in this group showed involvement of LV segments 1 and 2, with an additional 3 patients showing involvement of LV segment 3. There were no significant differences in the electrocardiographic findings: incidence of right bundle branch block, ventricular pre-excitation, or supraventricular tachycardia among these 2 groups.

The risk for an adverse clinical outcome was higher in group 1. Five of 10 patients (50%) in this group developed progressive LV dysfunction, of whom 3 (30%) died due to refractory congestive heart failure. Of the patients surviving beyond the neonatal period, the risk for progressive LV dysfunction was higher in group 1 (5 of 10 patients; 50%) compared with group 2 (4 of 51 patients; 8%) (relative risk: 6.375; 95% confidence interval: 2.06 to 19.66). The risk of death in group 1 was 30% (3 of 10 patients) versus 13% (7 of 51 patients) in group 2 (relative risk: 2.185; 95% confidence interval: 0.67 to 7.04).

We looked at the effect of LVNC on the outcome over short-term follow-up. Coexistent LVNC led to early diagnosis, often in utero as fetal hydrops or in the neonatal period as cyanosis, and presented with refractory heart failure leading to death in 30% in the neonatal period. In addition, over 50% of those surviving past the neonatal period developed progressive LV dysfunction requiring either medical therapy or additional interventions. In contrast, the mortality was relatively low (13%) in group 2, with 44 surviving patients and 2 patients (5%) developing progressive LV dysfunction due to dilated cardiomyopathy and requiring cardiac transplantation. Excluding deaths in the neonatal period, the relative risk for adverse outcome—either development of LV dysfunction, congestive heart failure, or death—was higher in group 1 versus group 2. Overall, patients with EA with no evidence of LVNC surviving past the neonatal period did well, with 95% remaining asymptomatic with normal ventricular function.

In summary, we noted a trend toward early detection and adverse outcome in group 1 patients. However, this study was limited by small numbers (10 patients), and we did not look at the severity of

EA as a contributory factor. LVNC is known to show a variable genotypic–phenotypic clinical expression, with mutations involving several genes, and whether any of these mutations represents a specific marker for EA or for a poor outcome is unknown. Our case series extends support for in-depth studies for better understanding of these 2 conditions (1).

Ricardo H. Pignatelli, MD,* Karen M. Texter, MD, Susan W. Denfield, MD, Michelle A. Grenier, MD, Carolyn A. Altman, MD, Nancy A. Ayres, MD, Subash Chandra-Bose Reddy, MD

*Division of Cardiology, MC 19345 C, Texas Children's Hospital, Houston, Texas 77030. *E-mail:* *cardop@bcm.tmc.edu*

http://dx.doi.org/10.1016/j.jcmg.2013.05.021

Please note: Drs. Pignatelli and Texter contributed equally to this work and are both first authors of the manuscript.

REFERENCE

1. Stahli BE, Gebhard C, Biaggi P, et al. Left ventricular non-compaction: prevalence in congenital heart disease. Int J Cardiol 2013;167:2477–81.