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R L. Larsen

P M. Applegate

D A. Dyar

P A. Ribeiro

S D. Fritzsche

*See next page for additional authors*



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# Dobutamine Stress Echocardiography for Assessing Coronary Artery Disease After Transplantation in Children

RANAE L. LARSEN, MD, FACC, PATRICIA M. APPLEGATE, MD, FACC, DANIEL A. DYAR, MA, PAULO A. RIBEIRO, MD, FACC, SHARON D. FRITZSCHE, RN, NEDA F. MULLA, MD, FACC, GIRISH S. SHIRALI, MD, FACC, MICHEAL A. KUHN, MD, FACC, RICHARD E. CHINNOCK, MD, AND PRAVIN M. SHAH, MD, FACC

*Loma Linda, California*

***Objectives.*** **The purpose of this study was to determine the feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography (DSE) for evaluating posttransplant coronary artery disease (TxCAD) in children, and to determine the frequency of selected cardiac events after normal or abnormal DSE.**

***Background.*** **Posttransplant coronary artery disease is the most common cause of graft loss (late death or retransplantation) after cardiac transplantation (CTx) in children. Coronary angiography, routinely performed to screen for TxCAD, is an invasive procedure with limited sensitivity. The efficacy of DSE for detecting atherosclerotic coronary artery disease is established, but is unknown in children after CTx.**

***Methods.*** **Of the 78 children (median age 5.7 years, range 3 to 18) entered into the study, 72 (92%) underwent diagnostic DSE by means of a standard protocol, 4.6 ± 1.9 years after CTx. The results of coronary angiography performed in 70 patients were compared with DSE findings. After DSE, subjects were monitored for TxCAD-related cardiac events, including death, retransplantation and new angiographic diagnosis of TxCAD.**

***Results.*** **No major complications occurred. Minor complications, most often hypertension, occurred in 11% of the 72 subjects. The sensitivity and specificity of DSE were 72% and 80%, respectively, when compared with coronary angiography. At follow-up (21 ± 8 months), TxCAD-related cardiac events occurred in 2 of 50 children (4%) with negative DSE, versus 6 of 22 children (27%) with positive DSE ($p < 0.01$).**

***Conclusions.*** **DSE is a feasible, safe and accurate screening method for TxCAD in children. Positive DSE identifies patients at increased risk of TxCAD-related cardiac events. Negative DSE predicts short-term freedom from such events.**

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Posttransplant coronary artery disease (TxCAD) is the leading cause of death beyond the first year after cardiac transplantation (CTx), and the most common indication for retransplantation in both children and adults (1,2). Most CTx centers perform coronary angiography (ANG) annually after CTx to screen for TxCAD. However, the angiographic appearance of TxCAD does not correlate well with either pathologic findings or the functional significance of the disease (3–5). The intimal hyperplasia found in TxCAD tends to be diffuse and concentric, making changes in the arterial lumen difficult to detect angiographically. Additionally, ANG is invasive and has risks of vascular injury and bleeding, especially in young children (6). A safe, sensitive and noninvasive method for detecting TxCAD would be invaluable for follow-up of children after CTx.

Dobutamine stress echocardiography (DSE) has been documented to safely, accurately and noninvasively detect atherosclerotic coronary artery disease (7–9) and determine its functional and prognostic significance (10–12). DSE, a noninvasive procedure, has important advantages over ANG, including lower cost, general availability and avoidance of radiation exposure. Although DSE has been performed to a limited extent in adult patients after CTx for surveillance of TxCAD (13–15), there is little experience with the procedure in transplanted or nontransplanted children. The purpose of this study was to determine the feasibility, safety and diagnostic accuracy of DSE in assessing TxCAD after CTx in children, and then to determine the frequency of selected cardiac events after normal or abnormal DSE.

## Methods

**Patient selection.** Patients were eligible for the study if they (1) underwent CTx at Loma Linda University Children's Hospital and Medical Center between the ages of 1 day and 17 years, (2) received annual follow-up at this institution, (3) were

From the Departments of Pediatrics, Cardiology, and Nursing, Loma Linda University School of Medicine, Loma Linda, California. This study was supported in part by the Loma Linda University Pediatric Endowment Fund, Loma Linda, California.

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Address for correspondence: Dr. Ranae L. Larsen, Division of Pediatric Cardiology, Loma Linda University Medical Center, Room 4433, Loma Linda, California 92354. email: rllarsen@ccmail.llu.edu.


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**Abbreviations and Acronyms**

ANG = coronary angiography
CTx = cardiac transplantation
DSE = dobutamine stress echocardiography
TxCAD = posttransplant coronary artery disease

at least 3 years of age at the time of the study, and (4) were at least 1 year after CTx. Patients were excluded if (1) they were pacemaker-dependent (with limited heart rate response to pharmacologic manipulation), (2) they had known or suspected rejection, (3) they were known to have severe TxCAD (because of initial safety concerns), or (4) informed consent was declined. The study protocol was approved by the Loma Linda University Institutional Review Board. Written informed consent was obtained from a parent or legal guardian, and when age-appropriate, from the patient.

**Patient population.** From November 1985 to December 1996, 292 children underwent cardiac transplantation at Loma Linda University. By the end of this study, in December 1996, there were 217 survivors. Of these, 34 were less than three years of age, 11 were less than one year after transplant, 82 were followed at institutions other than Loma Linda and 5 were pacemaker-dependent. Of the remaining 85 eligible patients, 78 (92%) were entered into the study. Seven patients were not studied because parents declined participation. In the study group, median age at CTx was 2 months (range 4 days to 16.0 years). Median age at the time of DSE was 5.7 years (range 3.0 to 18.0 years). Studies were performed 4.6 ± 1.9 years (range 1.0 to 9.0 years) after CTx.

At the time of DSE, the patients' immunosuppressive protocol included cyclosporine (n = 70), tacrolimus (n = 2), azathioprine or methotrexate (n = 42) and prednisone (n = 10). Some patients were receiving either a calcium antagonist (n = 10) or an angiotensin-converting enzyme inhibiting agent (n = 10) for treatment of systemic hypertension. No patient was receiving beta-adrenergic antagonistic therapy. Medications were given as per the patient's usual schedule on the morning of the test.

The CTx follow-up protocol at Loma Linda University Children's Hospital and Medical Center includes annual ANG beginning one year after CTx. Repeat transplantation is recommended when TxCAD becomes severe (>75% narrowing) in any one vessel. Patients with mild or moderate disease undergo ANG every 6 months.

**Dobutamine stress echocardiography.** All children younger than 6 years of age were sedated with chloral hydrate (60 mg/kg, maximum dose 1,200 mg) orally and midazolam (1 mg) intravenously for the study. Additional midazolam was then given as needed for anxiety during the study. Heart rate, blood pressure and oxygen saturation (by pulse oximetry) were monitored throughout the study.

Transthoracic echocardiographic imaging was performed on standard cardiac ultrasound equipment (Hewlett-Packard Sonos 1000 or 1500 or Acuson 128XP). Parasternal short and long axes and apical two- and four-chamber views of the left ventricle were obtained at baseline and during each stage. Images were recorded on videotape at each stage of dobutamine infusion. An on-line analysis system (Nova-Microsonics ImageVue DCR) was used for acquisition and digital analysis of images obtained at baseline, low dose, mid-dose and peak dobutamine dose. The rest and stress echocardiographic images were arranged in a quad screen display for simultaneous comparisons.

Dobutamine was begun at an infusion dose of 5 μg/kg/min intravenously and increased every 3 minutes in 5- to 10-μg/kg/min increments depending on individual patient response. The study was terminated if the patient (1) reached a maximum dobutamine dose of 50 μg/kg/min; (2) attained 75% of age-predicted (220 minus age in years) maximal heart rate; (3) developed new wall motion abnormalities in any segment; (4) became hypotensive, with a decrease in systolic blood pressure to <80 mm Hg; (5) became hypertensive, with an increase in systolic blood pressure to >180 mm Hg or diastolic blood pressure >100 mm Hg; (6) developed sustained supraventricular or ventricular arrhythmias, or (7) developed ≥2-mm ST segment depression on the 12-lead electrocardiogram. Although many DSE protocols recommend that a peak heart rate of 85% of age-predicted value be attained, a peak heart rate of 75% age-predicted value was chosen because of concerns for safety in this young population and known chronotropic incompetence secondary to cardiac denervation after CTx (16,17).

A cardiologist experienced in DSE was present during the performance of each study and interpreted the results. This investigator had no knowledge of the patients' clinical history or previous ANG. A normal response to dobutamine was defined as a progressive increase in myocardial wall thickening, wall motion, and left ventricular ejection fraction, and improvement in any resting wall motion abnormalities during dobutamine infusion. An abnormal response to dobutamine, indicating possible ischemia, was defined as a reduction in myocardial wall thickening or wall motion, failure of a resting wall motion abnormality to improve or failure of the ejection fraction to increase during dobutamine infusion. Specific qualitative descriptions of new wall motion abnormalities or other dobutamine-induced abnormalities were noted in a written report.

**Dobutamine stress electrocardiography.** Standard 12-lead electrocardiograms were recorded in all patients at rest, at the end of each dobutamine stage and during recovery. Electrocardiograms were monitored for rate, rhythm and for evidence of ischemia. The tracings were considered abnormal and suspicious for ischemia if there was a >1.5-mm ST segment depression compared with baseline.

**Coronary angiography.** Cineangiograms of each coronary artery in two orthogonal planes were obtained using the Judkins' technique through a percutaneous femoral artery approach. The left coronary artery was filmed in caudally angulated left anterior oblique and cranially angulated right

anterior oblique views, followed by a second injection using cranially angulated left anterior oblique and caudally angulated right anterior oblique projections. The right coronary artery was filmed in the right anterior oblique and left anterior oblique projections. A coronary vasodilator was not routinely given before contrast injection.

Seventy of the 72 children (97%) undergoing DSE underwent ANG and formed the basis for comparisons between results of DSE and ANG. In 2 children, the operator was unable to obtain arterial access. DSE was performed the same day as ANG in 40 patients. In the remainder, DSE was performed no more than 90 days before or after ANG.

Two investigators experienced in the interpretation of ANG performed visual qualitative assessment after CTx, one performing the study and a second from review of the cineangiograms alone. These investigators had no knowledge of the results of the DSE or of the results of previous ANG. If there was a difference in interpretation between the two investigators, the cineangiograms were reviewed by a group of experienced pediatric cardiologists and pediatric cardiothoracic surgeons. Evidence of TxCAD was recorded and graded for severity and distribution. Mild TxCAD was defined as <50% narrowing of any coronary artery branch. Moderately severe TxCAD was defined as 50% to 75% narrowing in any coronary artery branch. Severe TxCAD was defined as >75% narrowing of any coronary artery branch. Angiograms were also reviewed for loss of third-order branching and for the presence of myocardial bridging.

**Statistical analysis.** The sensitivity and specificity of DSE for detection of TxCAD was determined using established formulas. Results for continuous variables in the text and figures are expressed as mean ± SD. Student's *t* test was used to analyze differences between mean values. A chi-square test was used to compare proportions. Kaplan-Meier life-table estimates of cardiac event-free survival were used to summarize follow-up data. A p value <0.05 was considered significant.

## Results

**Feasibility.** Written informed consent was obtained for 78 children. Six (8%) were unable to be studied or were judged to have diagnostically inadequate studies. Of these six, dobutamine infusion was not begun in four children. Two children had poor acoustic images at baseline. One child had baseline hypertension >180/100 mm Hg. One patient had severe baseline wall motion abnormalities, and at the discretion of the monitoring cardiologist, the study was discontinued before dobutamine infusion was begun. This child was subsequently found to have severe angiographic TxCAD. Dobutamine infusion was terminated before a complete study could be performed in two other patients who developed severe hypertension at dobutamine doses of 5 μg/kg/min. Overall, 92% of the 78 children in whom consent was obtained underwent a technically diagnostic DSE.

**Table 1.** Baseline and Peak Dobutamine Stress Hemodynamic Data

| | Baseline | Peak Dobutamine Dose |
|---|---|---|
| Heart rate (beats/min) | 100 ± 16 | 159 ± 18* |
| Range | 57–135 | 96–193 |
| % predicted for age | | 75% ± 8% |
| Systolic blood pressure (mm Hg) | 105 ± 12 | 130 ± 21* |
| Range | 81–138 | 96–188 |
| Diastolic blood pressure (mm Hg) | 61 ± 14 | 68 ± 17 |
| Range | 31–92 | 31–105 |
| Heart rate–blood pressure product | 10.3K ± 2.9K | 20.1K ± 3.8K* |
| Range | 5.7K–13.7K | 13.0K–30.8K |

*$p < 0.001$. Data presented are mean value (range) ± SD.

**Safety.** Reasons for terminating the dobutamine infusion included (1) attainment of the target heart rate in 45 (63%) patients, (2) reaching the maximal dobutamine dose in 15 (21%) patients, (3) new or worsening wall motion abnormalities in 10 patients (14%), and (4) development of hypertension in 2 patients (3%).

No patient developed major complications during dobutamine infusion. Minor adverse effects were noted in 8 of 72 patients (11%). Hypertension was the most common adverse effect, occurring in 3 of 72 patients (4%). Blood pressure returned to normal within 15 minutes in all patients with no treatment, other than discontinuing the dobutamine. One patient became mildly hypotensive after the dobutamine infusion was discontinued. Two patients developed occasional (<3 complexes/min) supraventricular ectopic beats during dobutamine infusion. One patient complained of mild headache. No patient developed ventricular arrhythmias, supraventricular tachycardia, chest pain, dyspnea, nausea, vomiting or dizziness during dobutamine infusion or the recovery period.

**Hemodynamic response.** The peak dobutamine dose was 30 ± 10 μg/kg/min. Resting and peak dobutamine stress hemodynamic data are summarized in Table 1. The target heart rate (75% of the age-predicted value) was attained in 63% of patients. Systolic blood pressure increased 24% during dobutamine infusion. Diastolic blood pressure did not change significantly. The heart rate–systolic blood pressure product doubled during dobutamine infusion.

**Dobutamine stress electrocardiography.** The rhythm was sinus throughout the entire study in all 72 patients. Forty-six of the 72 patients (64%) had either right ventricular conduction delay or complete right bundle branch block on the baseline electrocardiogram. No patient had electrocardiographic changes with dobutamine infusion that met the criteria for ischemia. One patient developed ST-segment depression of 1 mm in leads $V_5$ and $V_6$. This patient otherwise had a normal response to dobutamine and normal ANG.

**Comparison of dobutamine stress echocardiography and coronary angiography.** Twenty-two of 72 patients (31%) had new wall motion abnormalities during dobutamine infusion, indicating possible ischemia. Coronary angiography demonstrated evidence of TxCAD in 14 of 70 children (20%).

**Table 2.** Coronary Angiographic and Dobutamine Stress Echocardiographic Results for Patients With Both Positive DSE and Coronary Angiography

| Patient | Location of DSE Abnormalities | Location and Severity of Coronary Angiography Abnormalities |
|---|---|---|
| 1 | Apical septum | Diffuse narrowing of LCA and RCA (mild) |
| 2 | Anterior septum and LV apex; apical anterior wall | Mid-LAD (mild) |
| 3 | Anterior and posterior septum | Distal LAD (moderate) |
| 4 | Mid- and apical septum; inferoapical segments | Cx (moderate); mid- and distal LAD (severe); RCA (moderate); first and second diagonals (moderate) |
| 5 | Posterior-inferior wall | Cx (moderate); distal LAD (mild) |
| 6 | Inferior wall | Cx (moderate) |
| 7 | Midanterior and apical septum | Distal LAD (moderate); second diagonal (moderate) |
| 8 | Posterior septum; inferoposterior segments | Cx (moderate); LAD (moderate); RCA (moderate) |
| 9 | Anterior septum | Mid- and distal LAD (moderate); Diffuse narrowing of RCA (mild) |
| 10 | Anterior septum; anterior apex | Cx (moderate); LAD (mild) |

Cx = circumflex coronary artery; DSE = dobutamine stress echocardiography; LAD = left anterior descending coronary artery; LCA = left coronary artery; RCA = right coronary artery

Comparisons of test results were made in the 70 patients who underwent both ANG and DSE. Dobutamine stress echocardiographic results were positive in 10 of 14 patients with angiographic TxCAD (sensitivity 71%) and negative in 45 of 56 patients with normal ANG (specificity 80%). Angiographic TxCAD was present in 10 of 22 patients (45%) with positive DSE (positive predictive value), and absent in 44 of 48 (92%) of patients with normal DSE (negative predictive value). The location and severity of the echocardiographic findings in the patients with abnormal ANG are described in Table 2.

There were no significant differences in age at CTx (median 2.0 vs. 2.4 months), age at DSE (median 5.4 vs. 6.0 years) or time since CTx (4.4 ± 1.8 vs. 4.8 ± 1.9 years) between the groups of patients with normal or abnormal DSE.

**Follow-up data.** The 72 patients who underwent DSE have been followed 21 ± 8 months since DSE (range 6 to 35 months). The four patients with positive ANG, but normal DSE ("false" negative studies), have subsequently had normal ANG 9 to 15 months after DSE. Review of the initial ANG suggested that the arteries interpreted as narrowed were areas of spasm rather than TxCAD. These four patients are alive and without evidence of TxCAD 29 to 34 months after initial ANG and DSE. The remaining 10 patients with both positive ANG and DSE have had confirmation of the coronary lesions by repeat angiographic or pathologic evaluation after death or retransplantation.

Figure 1 compares the freedom from death, retransplantation for TxCAD or new angiographic evidence of TxCAD after normal versus abnormal DSE. At follow-up, 4% of the 50 patients with normal DSE had TxCAD-related late cardiac events compared with 27% of patients with abnormal DSE.

## Discussion

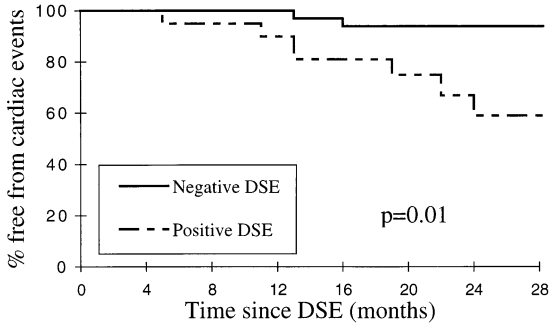
**Transplant coronary artery disease.** Posttransplant coronary artery disease is an important cause of morbidity and mortality after CTx in children, occurring in 12% to 24% of recipients at 1 year and in 18% to 43% of recipients at 3 years after CTx (18–22). At our institution, the incidence of TxCAD was 23% seven years after CTx in patients transplanted during infancy for hypoplastic left heart syndrome (23). Once TxCAD is evident angiographically in adults or children, short-term mortality is high (24,25), making surveillance a high priority.

Risk factors associated with TxCAD in children have not been completely defined. A study of 206 children who underwent transplantation at our institution who survived more than one year indicated that only severe rejection beyond the first post-CTx year and the number of rejections in the first six months after CTx were independent predictors of TxCAD (25). Gender, age at CTx, lipid status, infection history and cytomegalovirus infection were not independent risk factors for the development of TxCAD.

Because of surgical cardiac denervation at the time of CTx, angina rarely occurs as a warning symptom of myocardial ischemia. Sudden death is often the first evidence of TxCAD. Many institutions perform yearly ANG to monitor for the development and progression of TxCAD, although the relative insensitivity of ANG compared with pathologic or intravascular ultrasound is well recognized (4,5,26). Additional disadvantages of ANG include the risk of vascular injury, particularly in children (27,28), exposure to radiation and the cost of the procedure.

**Dobutamine stress echocardiography.** This procedure has been used to a limited extent in adults after CTx, with a sensitivity and specificity of 83% to 95% and 55% to 91%, respectively, when compared with ANG (13–15). Spes and coinvestigators (14) reported the sensitivity of DSE to be 79%

**Figure 1.** Kaplan-Meier event-free curves for posttransplant coronary artery disease (TxCAD)–related cardiac events, including death, retransplantation and the new development of angiographic TxCAD according to positive or negative dobutamine stress echocardiography (DSE). Each plot represents the proportion of patients remaining event free.



when compared with intracoronary ultrasound. Derumeaux et al (13) advocated that DSE be performed as routine surveillance for TxCAD in adult patients after CTx. Studies have also suggested that DSE predicts risk of cardiac events in adult CTx recipients (29,30). Akosah and coinvestigators found that after 24 months of follow-up, 33% of patients with positive DSE had experienced TxCAD-related cardiac events.

**Dobutamine stress echocardiography in children.** Experience with DSE in children is limited (31,32). Kimball and Witt (32) performed 74 DSE studies in 46 children, 10 of whom underwent the study after CTx. Four of the 10 patients had evidence of dobutamine-induced ischemia (33). All four of these patients were documented to have TxCAD at follow-up.

**Present study.** *Feasibility.* Our study shows that DSE is feasible in most children after CTx. Because the quality of the echocardiographic images is important for accurate interpretation of wall motion abnormalities (34), the smaller size and therefore better imaging windows of children may offer an advantage. The cooperation of younger patients was facilitated by our use of sedation. In older children, we found that a clear, simple explanation of the procedure usually resulted in their cooperation and tolerance of the procedure.

*Safety.* The most common adverse effect was hypertension, which resolved after dobutamine was discontinued. No complications secondary to ischemia occurred, even in children with angiographic TxCAD. By study design, patients with known severe (>75% narrowing) TxCAD were excluded. Thus, safety of DSE in patients with severe TxCAD cannot be addressed by this study.

*Diagnostic accuracy.* Compared with ANG performed near the time of DSE, the sensitivity of DSE in our study was similar to that reported in adult patients with atherosclerotic coronary artery disease. Because the four patients with "false negative" DSE were ultimately determined to have coronary artery spasm rather than TxCAD, all patients with angiographic evidence of TxCAD had an abnormal DSE. Additionally, approximately one fourth of patients with "false positive" DSE died suddenly and had coronary artery disease at pathologic evaluation.

Previous observers have emphasized the importance of experience and competence in interpreting stress echocardiograms (35). Because coronary artery disease is relatively uncommon in children, many pediatric cardiologists may be unaccustomed to assessing echocardiographic ischemia-induced wall motion abnormalities. Assistance from practitioners experienced in the performance and interpretation of these studies can be the key to accurate interpretation.

*Prognostic value.* The most important contribution of DSE in this population may be its identification of children at increased risk for the development of TxCAD and its complications. By two years after abnormal DSE, graft loss, either by death or repeat CTx, occurred in 40% of patients. In contrast, patients with normal DSE had only a 4% risk of TxCAD-related cardiac events in the same time period. The experience in two children with both normal ANG and DSE 15 to 18 months before dying suddenly of TxCAD, however, emphasizes the importance of systematic monitoring of patients after CTx.

We propose that after CTx, children undergo annual DSE to screen for TxCAD. An experienced echocardiographer should interpret the studies. Coronary angiography may be performed less frequently, barring a late rejection episode or clinical symptoms suggestive of coronary artery disease. This may result in reduced morbidity and expense of follow-up after CTx. Children with abnormal DSE, however, should undergo an invasive study such as ANG or intravascular ultrasound. Our institution has changed its CTx follow-up protocol to include yearly DSE, and ANG every other year, beginning one year after CTx. Follow-up is needed to determine the impact of this change on patient morbidity, survival and cost.

**Study limitations.** This study was limited by our use of qualitative ANG as the reference standard for comparison of the results of DSE. Although it is the method most often used for assessment of TxCAD, ANG is an imperfect standard because of its recognized limitations in sensitivity. Intracoronary ultrasound, which may be the new gold standard for the detection of TxCAD, is expensive, invasive and has significant limitations in small vessels (36,37). DSE is noninvasive and can usually visualize all segments of the myocardium.

DSE is limited by its reliance on the subjective analysis of images by the observer (38,39). However, other investigators have reported interobserver variability to be low, with interobserver agreement of >90% (40,41). Additionally, the reliability of DSE when interpreted by experienced observers has been established by several large studies (38).

**Conclusions.** We conclude that DSE safely and noninvasively provides accurate diagnostic and prognostic information regarding TxCAD in children after CTx. Patients with abnormal DSE have a high likelihood of TxCAD-related cardiac events in the 24 months after DSE. Patients with normal DSE have an excellent prognosis in the same time period. We propose that DSE be performed yearly in children after CTx for surveillance of TxCAD.

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