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Serial Dobutamine Stress Echocardiography for Detection of Cardiac Allograft Vasculopathy

Christoph H. Spees, Harald Mudra, Susanne D. Schnaack, Johannes Rieber, Florian Fischle, Thomas M. Krüger, Ulrike Klaus, Peter Überfuhr, Bruno Mauermann, Christian E. Angermann, Cornelia Pflaum, University of Munich, Germany.

Dobutamine stress echocardiography (DSE) is a noninvasive and safe test to detect myocardial ischemia. To analyse, if DSE is feasible for assessment and follow up of coronary allograft vasculopathy (CAV), 13 patients (P; 50 +/- 8 years, 60 +/- 32 months after heart transplantation) were studied in 2 consecutive routine annual investigations by coronary angiography (ANGlO). CAV was evaluated as an increase in IVUS and/or angiographic luminal diameter of intimal hyperplasia, modified Stanford grading, grades 1-6) and dobutamine stress echocardiography (DSE, 5-40 mcg/kg/min, 5 min stages). Regional wall motion abnormalities (WMA) were assessed qualitatively (2-D-echo, 16 segment model) and quantitatively (M-Mode, systolic thickening of interventricular septum (IVS) and LV posterior wall (LPW)).

Results: P were allocated to 2 groups: group 1, normal DSE at entry (n = 9); group 2, WMA during DSE at entry (n = 4). At the initial study, no P had WMA at rest. In group 1, IVUS revealed only mild intimal hyperplasia (maximal thickening of intima-media: 3.0 ± 0.7 mm). In group 2, IVUS was completely normal in 9P and showed mild dilating angiopathy in 1P. 9P developed WMA during DSE (total, 12/64 segments); ANGIO was normal in all P. IVUS grades were 12/7/4/0.5/0.5. Mean systolic thickening of IVS (rest, 26 vs. 32%; max. DSE, 37 vs. 63%; group 2 vs. 1) and LPW (rest, 35 vs. 57%; max. DSE, 65 vs. 95%) were smaller in group 2 than in group 1. At follow up, 3/9 group 1P had DSE-induced WMA (9/144 segments); all had IVUS progression to grade ≥ 3.5, but no ANGIO changes. In group 2, 1P with stress induced WMA in only one segment at entry was judged normal at follow up (IVUS: 1.2 and 1.6, respectively; false positive DSE at entry). 3 group 2P deteriorated: 1 had diffuse WMA at rest (max. IVUS grade 4) and 2 had diffuse WMA at IVUS (total, 26/48 segments). Mean IVUS grades rose to 4.05/5.6/0; ANGIO remained normal in 2P and showed diffuse rarefaction of small vessels in 1 P.

Conclusion: All P with marked-to-severe intimal hyperplasia assessed by IVUS and/or marked ANGIO findings were identified by DSE. Serial DSE is a feasible and safe method for noninvasive screening and follow-up for CAV in heart transplant recipients. In P with normal DSE, the need for routine ANGIO at regular intervals may be reduced.

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Relationship of Donor Age and Pre-existing Coronary Disease by Angiography and Intracoronary Ultrasound to Later Development of Cardiac Allograft Coronary Artery Disease


The increasing demand for cardiac donors has led to a tendency to liberalize the criteria for donor acceptance. Since cardiac allograft coronary artery disease (TxCAD) is the major complication limiting long-term post-transplant survival, we analyzed a series of 242 consecutive cardiac transplant patients (Txpts) who had baseline early post-op coronary angiograms and a subset of 41 pts with baseline intracoronary ultrasound (ICUS) to determine whether either older donor age or pre-existing CAD at the time of transplantation influenced the later occurrence of TxCAD. Fourteen pts had angiographic evidence of some pre-existing CAD (donor CAD group); the other 228 did not (no donor CAD group). New disease was defined either development of new obstructive lesions or progression of old lesions on serial annual angiograms. Freedom from new disease was 97%, 89%, and 77% in the no donor CAD group (p = 0.003) vs. 86%, 86%, and 77% in the no donor CAD group (p = 0.003). No donor CAD pts were subdivided into older (≥40) and younger (<40) groups. Freedom from TxCAD was 92%, 52%, and 43% at 1, 3, and 5 years post-op in the older group (n = 31, mean age 49) vs. 97%, 82%, and 53% in the younger group (n = 184, mean age 24) (p = 0.003) (Mantel-Haenszel).

Baseline ICUS imaging revealed baseline class 3 lesions in 7 of 9 older donor hearts, and in only 7 of 32 younger donor hearts (p = 0.006). Three of these 14 ICUS class 3/4 pts later developed TxCAD vs. only of 27 class 1/2 pts at baseline (p = NS). Older donor age, no calcium blocker use and pre-existing CAD were significant predictors for development of TxCAD (p = 0.0006, 0.0003, and 0.0033 respectively, Cox regression analysis).

Conclusion: (1) Older donors or pre-existing CAD have a greater tendency to develop TxCAD, (2) ICUS reveals moderate to severe intimal thickening not angiographically detectable and there is a trend toward such disease later to TxCAD.

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Extent of Coronary Myointimal Proliferation and Its Relationship to Resistance Vessel Function in the Cardiac Allograft

Thomas Wolforth, Thomas J. Donohue, John H. Drury, Richard G. Bach, Eugene A. Caraccio, Andrew S. Potash, Stephen H. Jannissel, Morton J. Kern, Pamela S. Perg. St. Louis University Medical Center, St. Louis, MO.

Transplant coronary arteriopathy is the major obstacle to long-term survival of cardiac allografts and is characterized by myointimal proliferation involving both epicardial conduit vessels and intramyocardial resistance vessels. To evaluate the relationship between gross donor heart morphology and myointimal proliferation, we enrolled 105 cardiac transplant recipients in P with normal DSE, the need for routine ANGIO at regular intervals may be reduced.

Results: P were allocated to 2 groups: group 1, normal DSE at entry (n = 9); group 2, WMA during DSE at entry (n = 4). At the initial study, no P had WMA at rest. In group 1, IVUS revealed only mild intimal hyperplasia (maximal thickening of intima-media: 3.0 ± 0.7 mm). In group 2, IVUS was completely normal in 9P and showed mild dilating angiopathy in 1P. 9P developed WMA during DSE (total, 12/64 segments); ANGIO was normal in all P. IVUS grades were 12/7/4/0.5/0.5. Mean systolic thickening of IVS (rest, 26 vs. 32%; max. DSE, 37 vs. 63%; group 2 vs. 1) and LPW (rest, 35 vs. 57%; max. DSE, 65 vs. 95%) were smaller in group 2 than in group 1. At follow up, 3/9 group 1P had DSE-induced WMA (9/144 segments); all had IVUS progression to grade ≥ 3.5, but no ANGIO changes. In group 2, 1P with stress induced WMA in only one segment at entry was judged normal at follow up (IVUS: 1.2 and 1.6, respectively; false positive DSE at entry). 3 group 2P deteriorated: 1 had diffuse WMA at rest (max. IVUS grade 4) and 2 had diffuse WMA at IVUS (total, 26/48 segments). Mean IVUS grades rose to 4.05/5.6/0; ANGIO remained normal in 2P and showed diffuse rarefaction of small vessels in 1 P.

Conclusion: All P with marked-to-severe intimal hyperplasia assessed by IVUS and/or marked ANGIO findings were identified by DSE. Serial DSE is a feasible and safe method for noninvasive screening and follow-up for CAD in heart transplant recipients. In P with normal DSE, the need for routine ANGIO at regular intervals may be reduced.

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Impact of Ischemia Time on Vascular Rejection and Expression of Peptide Growth Factors in Transplant Arteriosclerosis

J. Wattenberger, T. I., L. A. Kikuy, Z. A. Wanders, B. Fellenström, K. Funas, 1 Dept. of Medicine, Ulm University Medical Center, Ulm, 2 Ludwig Institute for Cancer Research and Uppsala University, Uppsala, S.

Accelerated arteriosclerosis in transplanted organs represents the major cause of graft failure and is limiting the clinical outcome of heart transplantation.

Using a rat aorta transplant model the impact of cold ischemia time up to 24 hours (extracorporeal storage time) and reperfusion injury upon development of transplant arteriosclerosis was analysed during the first 2 months after transplantation both in allogenic as well as in syngenic transplants. The expression of the various isoforms of transforming growth factor beta (TGF-beta) latent TGF-beta binding protein (LTBP) as well as platelet-derived growth factor (PDGF) and its receptors were studied using immunohistochemistry, followed by a semi-quantitative evaluation and multivariate analysis (n = 18 for each antiserum).

In the syngeneically transplanted aortas the expression of TGF-beta (p < 0.03), PDGF-BB (p < 0.05) and of the PDGF-alpha receptor (p < 0.05) in the neointima increased significantly with the extent of cold ischemia time. Furthermore, there was a significant induction of LTBP (p < 0.05) correlating with the observation time after transplantation. In the allogeneic aortic grafts, expression of all examined protein was increased soon after transplantation. In summary, TGF-beta and PDGF are induced by allogeneic as well as ischemic stimuli in transplanted vessels. Moreover, in the syngeneic transplant model, cold ischemia time prior to implantation has an impact on the expression of growth factors and the extent of vascular remodeling.