Antibody Mediated Rejection (AMR) in Cardiac Transplantation
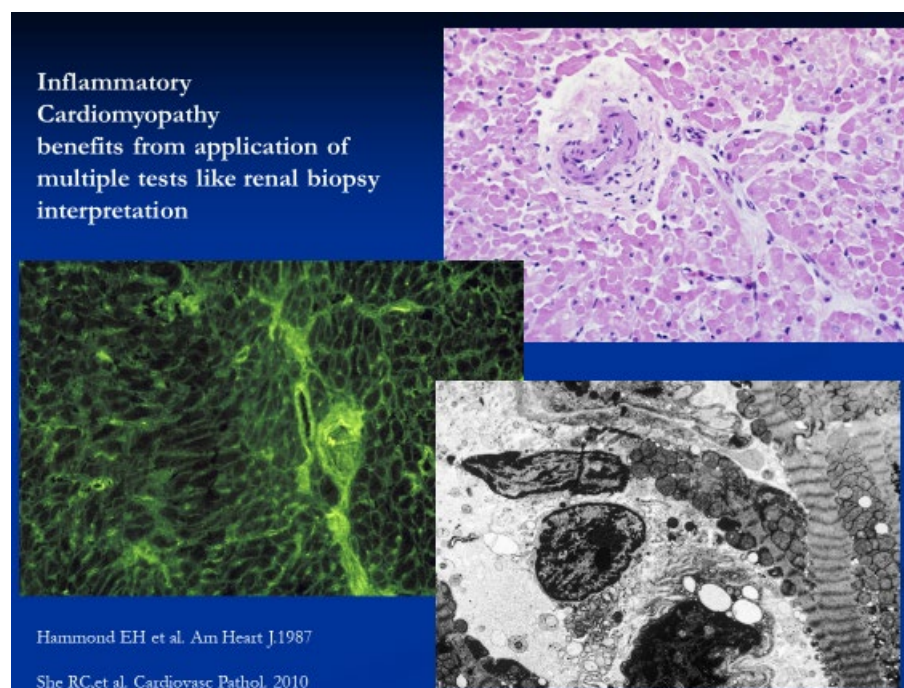*Author: Elizabeth Hammond, MD*

When the UTAH Cardiac Transplant Program began in 1985, it was believed that all rejection was mediated by lymphocyte killing of muscle cells in the heart: so called cellular rejection or ACR. Immunosuppressive therapy targeted this form of rejection and was becoming more and more effective. However, a few patients did not display typical pathologic features and quickly developed heart failure or died. We wondered whether this process could be mediated by another type of rejection, that involving antibody accumulation in the heart capillaries and damage based on poor blood supply (ischemic damage). Published work had already shown that antibodies against the kidney could circulate in the blood of kidney transplant recipients and such recipients often lost their grafts.

In our program we adopted pathology practices that had become standard for looking at kidney biopsies and kidney transplant biopsies. Biopsies were subjected to routine histologic evaluation but also had testing of frozen tissue for markers of antibody localization in the heart (IF testing). Earlier work in our laboratory had shown that native heart biopsies occasionally had antibodies localized to capillaries or interstitial regions and often those patients had heart failure and evidence of ischemic damage by specialized testing (diagnostic electron microscopy)

Inflammatory
Cardiomyopathy
benefits from application of
multiple tests like renal biopsy
interpretation

Hammond EH et al. Am Heart J.1987

She RC,et al. Cardiovasc Pathol. 2010

In this collage from a study of native heart biopsy pathology in 1987, three tests like those performed on renal biopsies are shown from one specimen. There is spotty interstitial mononuclear cell infiltration by Hematoxylin and Eosin staining (top), accumulation of interstitial and vascular complement (C3) by Immunofluorescence microscopy (left) and obvious endothelial cell injury and macrophage infiltration by electron microscopy (right).

These techniques had never been applied to heart transplant biopsies. We applied the techniques, using semiquantitative scoring of findings on both the histologic and IF testing and entering our results into a database created for that purpose. In 1989, we reviewed our results, linking the pathology findings to patient outcomes after transplant. We found that those patients with antibodies localized to their hearts were more likely to experience graft loss or death. We called this process acute vascular rejection or later acute antibody mediated rejection (AMR) We also reported on another new type of rejection which was a mixed form including both ACR and AMR. This type of rejection was not recognized by others until 2011.
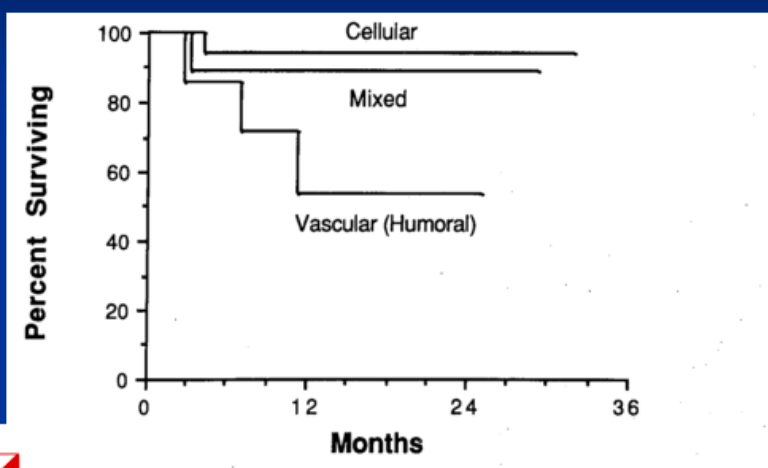
Original survival analysis conducted on 36 consecutive patients from our center in 1989. Patients were prospectively categorized as to rejection pattern before survival data was accessed. Patients were considered to be vascular (AMR) rejectors if they had at least 3 episodes of pathologic findings of AMR within the first 3 months post-transplant, regardless of clinical status. Patients with vascular rejection pattern (AMR) had a significantly worsened survival at up to 3 years of follow-up. (p=<0.05)

Based on this work, we devised a grading schema for AMR in 1992 and used that schema to categorize our patients in the database so that further research could be done. Acute cellular rejection has been the subject of a consensus grading scheme in 1991.
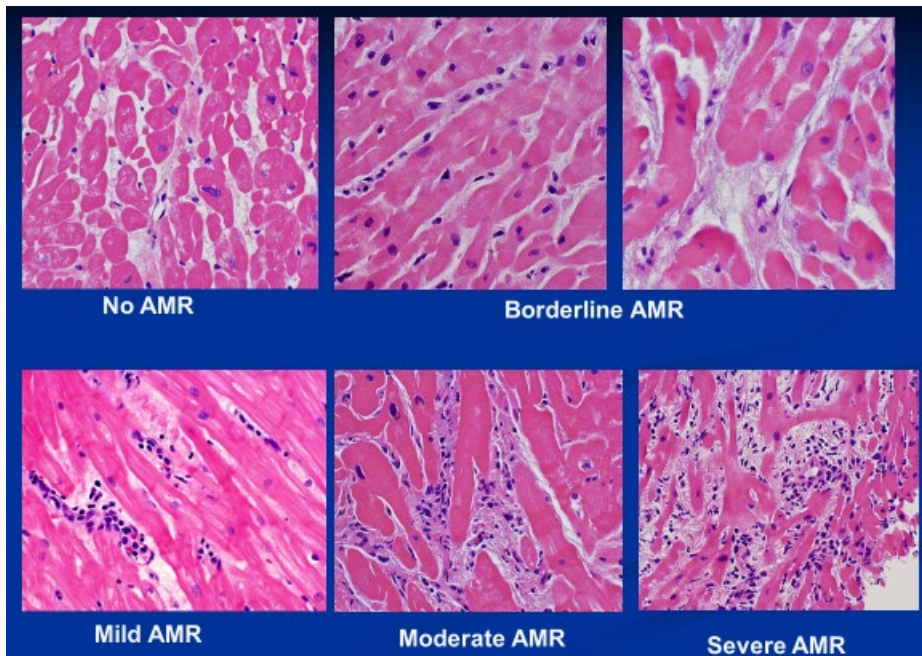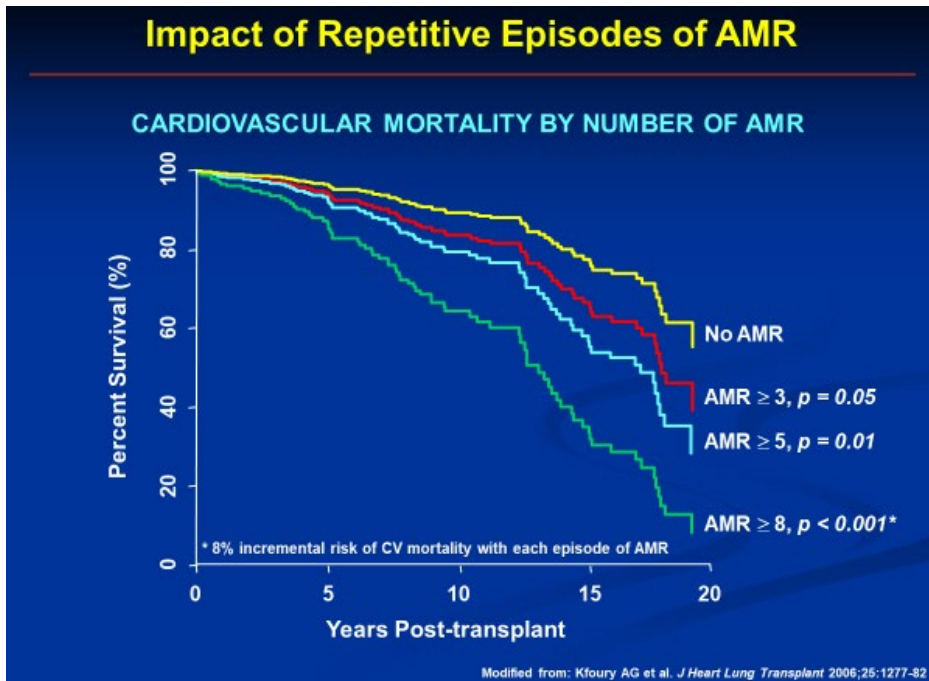
This collage illustrates the features of various grades of vascular (now AMR) rejection by histologic examination classified by the "Utah" grading system proposed and published in 1992. Specific pathologic features (including histologic and immunofluorescent findings) are graded and then used to define a grade of rejection. Since 1986, all such pathologic parameters are captures on each biopsy and kept in a research database to facility investigation and modification of the grading schema over time.
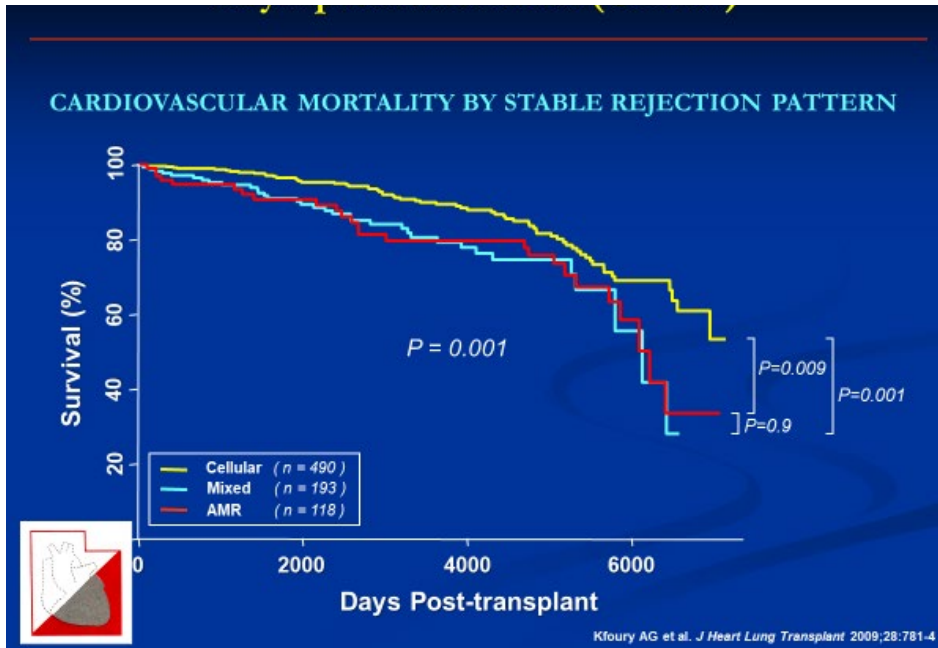
Despite publication of our findings, our results were not adopted by other programs who refused to believe our results. Nevertheless, we continued to study this process and publish our findings.

We learned that AMR was more common in patients who had circulating antibodies in their blood prior to transplant, in women, especially those who had borne children, in patients with positive cross matches indicating a mismatch of blood type at transplant, and in young patients who had stronger immune systems. We also learned that patients with antibody mediated rejection were more likely to develop coronary artery disease (CAV), the most common reason for late failure of heart transplants. Patients with AMR were much more likely to die than those without this process in three sequential reviews of our data. Patients who had repeated episodes of AMR were much more likely to die, even when the AMR was not associated with clinical symptoms.

Impact of Repetitive Episodes of AMR

CARDIOVASCULAR MORTALITY BY NUMBER OF AMR

No AMR

AMR ≥ 3, *p = 0.05*

AMR ≥ 5, *p = 0.01*

AMR ≥ 8, *p < 0.001**

* 8% incremental risk of CV mortality with each episode of AMR

Modified from: Kfoury AG et al. *J Heart Lung Transplant* 2006;25:1277-82

This expanded survival analysis on our patient cohort in 2009 (869 patients) illustrates the profound impact of repetitive episodes of antibody mediated rejection on patient outcome over up to 20 years. One episode according to our nomenclature, consists of diagnostic pathologic features of AMR found on a single biopsy. Clinical status was not used to define status. This definition of AMR came to be known as 'pathologic antibody mediated rejection' (pAMR) in the consensus schema adopted by the International Society of Heart and Lung Transplantation in 2013.

CARDIOVASCULAR MORTALITY BY STABLE REJECTION PATTERN

P = 0.001

P=0.009

P=0.001

P=0.9

Cellular (*n = 490*)
Mixed (*n = 193*)
AMR (*n = 118*)

Kfoury AG et al. *J Heart Lung Transplant* 2009;28:781-4

This survival analysis, published on our 869 patient cohort in 2009, demonstrates again the adverse survival impact of AMR as defined by our publications. Finding AMR on a single biopsy regardless of clinical status at the time, constitutes one episode of AMR. We defined the pattern of AMR as having 3 biopsies with AMR findings. This pattern of AMR was found to adversely affect patient outcome in 2009 as it had been shown to do in 1989 and 2006 in previous analyses.

We continued to publish our findings and present these concepts at national and international meetings, where they were met with skepticism. Finally, in 2004, a national conference was held about antibody mediated rejection of the heart, lung, and kidneys because, despite very effective immunosuppression treatments, many patients were dying of a process increasingly attributed to antibody mediated rejection. At that conference, our work was highlighted and new standards for classification of AMR were discussed and finally approved in 2011. In the meantime, other investigators at UCLA and Cleveland Clinic were able to corroborate our findings. Using the newly devised classification scheme for AMR in the heart, we were able to publish findings that documented the value of the new schema.
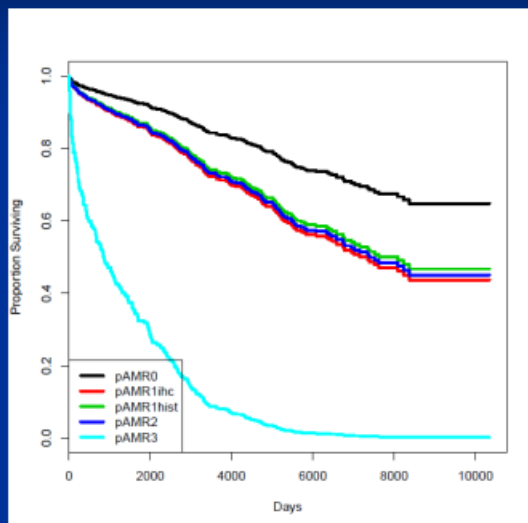

This analysis of 13,812 biopsies on 1014 patients transplanted on our program from 1985-2014 validated the consensus pAMR grading schema proposed by the International Society of Heart and Lung Transplantation in 2013. Since 1985, pathologic features and clinical outcomes of all patients were recorded and stored in a database that allowed regrading of biopsies because specific features were independently graded on each biopsy. This analysis documented the adverse impact of AMR on patient outcome. In the consensus schema, pAMR is regarded as a diagnosis on a single biopsy.

Asymptomatic AMR (UCLA)

5-Year Freedom from CAV
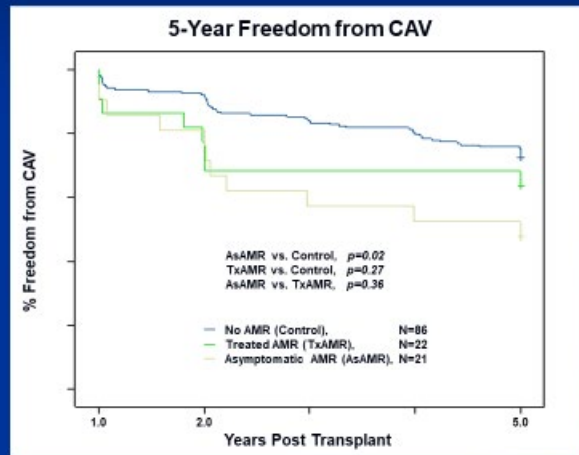
Wu GW et al. *J Heart Lung Transplant* 2009;28:417-22

A survival analysis conducted on 43 heart transplant patients at UCLA with AMR confirmed our findings that AMR was associated with significant adverse outcomes. In their analysis Wu et al used freedom from allograft vasculopathy (CAV) as the outcome variable.

Abdallah (Boudi) Kfoury, MD; Elizabeth Hammond, MD; Josef Stelhik, MD, MPH

The value of our work was recognized by the International Society of Heart and Lung Transplantation Pioneer award in 2011.