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EDITOR'S PAGE

# On Fishing Expeditions, Laws of Fishing, and Good Fishermen...

Jagat Narula, MD, PhD,* William A. Zoghbi, MD,† Y. Chandrashekhar, MD, DM‡

The genesis of good research is based on critical observations, but the way these observations come about seems to generate a social-status hierarchy in the medical research community. Traditionally, successful research is viewed as a well deserved fruit of a neat a priori hypothesis, great toil, meticulous experiments, and a juggernaut of logical reasoning. Serendipitous discovery, a previously unknown finding that an investigator chances upon while testing a primary hypothesis, occupies a slightly lesser standing in this hierarchy. However, since there have been numerous examples of such success and since the investigator deserves credit for keeping his eyes open to the unexpected finding, this kind of research is also often lauded. On the other hand, a fishing expedition, which explores some possible relation between several variables while often hoping wildly that something interesting would show up, is considered to be of a diminished pedigree. Scientists in general, and grant funding agencies as well as journal editors in particular, have viewed it with disdain, even though such findings may help move the field forward.

While we, as editors, are also commonly prey to this line of thinking, we often encourage ourselves to be open to such studies if the data are really intriguing. One could also argue that research in general is quite unpredictable, and a fishing expedition, like many things in life, may not necessarily be a bad thing; such efforts may pay off if something interesting is captured and the ability to handle enormous amounts of data might make such explorations even more useful. This has already happened in genomics and proteomics and is being increasingly seen in metabolomics. Indeed, the ever expanding computing power provides insights that could not be possible with traditional methods of fishing—*a la* the reenactment of the differences between gill-net fishing versus traditional hook, line, and sinker methods. We will be seeing more fishing expeditions in future medical research, and journals, despite some damage to their perceived prestige, will eventually be more open to publishing such studies.

Of course, such forays need an extreme amount of caution. Fishing expeditions exponentially increase the likelihood of false-positive and nonreplicable results and introduce bias. This should just make us increase the scientific protection to ensure validity of data rather than discourage its use altogether. There are many ways to be conservative about outcomes in fishing expeditions including robust statistical methodology to limit the number of catches that can be considered "keepers" (1). The greater the number of relationships tested, the more conservative we have to be in order to preserve the validity of observations. As good fishermen know, too much technology or too many lines can often snag a lot of junk. The cause and effect relationships of such findings, even though optimistically espoused by their authors, are nearly always unclear. A large number of associations will be red herrings and will engender unfruitful investigations with loss of time and wasted resources. Finally, such data will be considered nondefinitive, and will have to pass the scrutiny of more rigorous hypothesis-based experimentation. The natural ferment of science is needed to finally determine if the results were real or random.

From the *Division of Cardiology, University of California Irvine, Irvine, California; †Cardiovascular Imaging Institute, Department of Cardiology, The Methodist DeBakey Heart and Vascular Center, Houston, Texas; and the ‡Division of Cardiology, VA Medical Center and University of Minnesota, Minneapolis, Minnesota.

The report by Eleid et al. (2) in this issue of *iJACC* might be an example of such a preliminary exploration. This study characterizes the serial changes in left ventricular (LV) function for transplanted hearts, wherein the transplant recipients demonstrated an improvement in global longitudinal strain within the first 3 months after transplantation. This functional improvement was associated with reduced combined risk of death and hospitalization compared with those who showed persistent strain abnormalities (Fig. 1). Interestingly, patients with abnormalities in LV mechanics exceeded the number of patients with biopsy-proven findings of acute cellular rejection. This is consistent with previous data where the global estimate of myocardial damage detected by myocardial uptake of radiolabeled monoclonal antimyosin antibodies exceeded that seen in endomyocardial biopsy specimens (3,4) (Fig. 2). During the first few months after heart transplantation, patients invariably showed myocardial uptake of monoclonal antimyosin antibody, revealing the presence of active myocardial damage. A gradual decrease in myocardial uptake was later observed that was paralleled by a progressive reduction in the number of rejection episodes in biopsy; this was considered to represent development of tolerance to the graft. Within the first 3 months (as also reported by Eleid et al. [2]), a substantial decrease in antimyosin antibody uptake was observed in most patients; this resolution of radiotracer uptake was associated with an uneventful course, and less need for maintenance-dose steroids and the number of endomyocardial biopsies. On the other hand, a handful of patients showing persistence of uptake or an increasing pattern of antimyosin antibody uptake predicted an increased number of cellular and vascular rejection episodes, likelihood of complications, necessity for retransplantation, and increased need for additional immunosuppressive agents and dependence on steroids (3) (Fig. 2). This novel confluence of observations highlights the phenomenon of retrodiction where older data are paralleled by another imaging modality achievable more easily; the advantage indeed being that retrodiction confirms that the current expedition should be free of experimental bias. Although a logical result was observed in the study by Eleid et al. (2) and the primary hypothesis was vindicated in this retrospective evaluation, they further explored the clinical determinants of persistent LV dysfunction at 1-year after cardiac transplantation by correlating multiple clinical and genetic variables with LV deformation. This exploration revealed an intriguing relationship of genetic expression profile as an independent predictor of global LV strain at 1-year after transplantation. On examining the individual components of the standard genetic test employed for the prediction of allograft rejection, the correlation of LV deformation with gene expression score was seen to be primarily driven by gene coding for semanophorin (SEMA 7A), a membrane-tethered cell signaling molecule which functions in neural development and macrophage

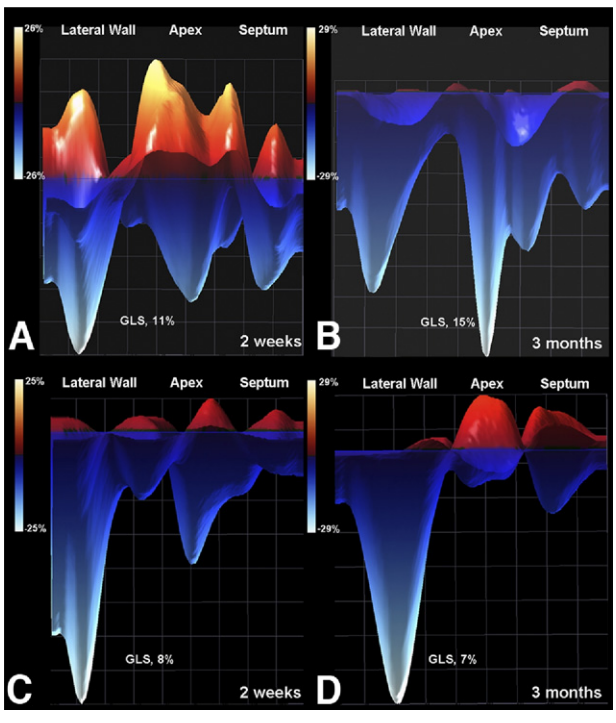


**Figure 1. Serial Changes in Longitudinal Strain After Cardiac Transplantation**

Color coded display shows the distribution of regional segments on x-axis and amplitude of longitudinal strain on y-axis. The time scale represented on the z-axis has been flattened in the 3-dimensional volumetric display for focusing on spatial variations in longitudinal strains. **A** and **B** illustrate a patient with improvement in longitudinal strains due to reduction in stretch **(red)** and improvement **(blue)** in longitudinal shortening strains at 3 months, whereas **C** and **D** illustrate a patient with lack of improvement in longitudinal strains. Note the reduction in shortening strains and increase in stretch in the septum. The allograft recipients, such as in **panels A** and **B**, showed an uneventful course. Figure courtesy of Partho P. Sengupta, MD, Mayo Clinic Arizona, Scottsdale, Arizona.

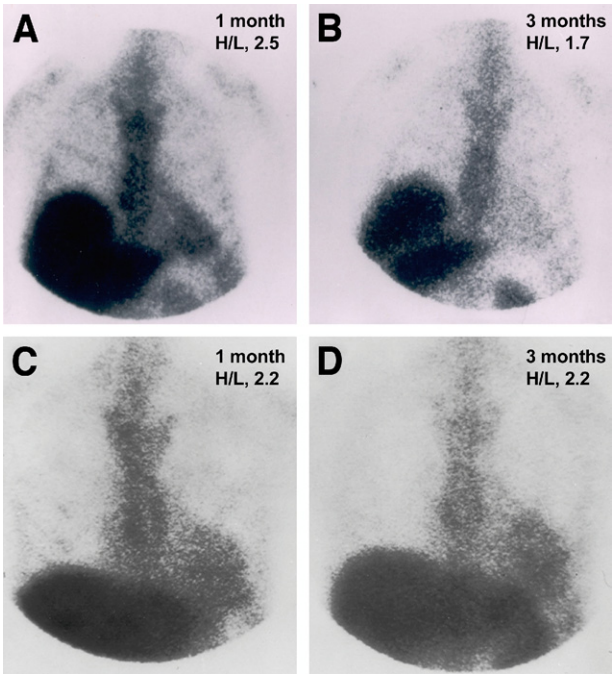


**Figure 2. Serial Changes in the Indium-111-Labeled Antimyosin Antibody Uptake After Transplantation**

Antimyosin antibody uptake represents the presence of myocardial necrosis, and a semi-quantitative extent of myocardial damage is assessed by calculation of heart-to-lung (H/L) ratio of the radiotracer uptake. The tracer uptake is invariably seen after the transplantation which resolves gradually thereafter and parallels the rate of development of tolerance. The antimyosin studies from 2 allograft recipients **(top and bottom)** are presented at 1 **(left)** and 3 **(right)** months after the transplantation. **Panels A** and **B** represent resolving antimyosin antibody uptake that predicted an uneventful course. **C** and **D** represent persistent antibody uptake; the post-transplantation course was riddled with numerous complications. Figure courtesy of Manuel Ballester-Rodes, MD, and Ignasi Carrio, MD, Barcelona, Spain.

and T-cell activation pathways. This relationship parallels recent reports where semanophorins have been suggested to modulate transmural mechanics (5). Semanophorin has also been implicated in reinervation of the allograft, which is known to influence myocardial performance after transplantation. The uncharted exploration in the Eleid et al. (2) study thus seems to fit nicely with some observations from other studies; indeed more of such collateral evidence may close the loop of possibilities. One could argue that there is sufficient biological plausibility about the data and further research into this line of thinking seems justified. In addition to demonstrating the validity of this unexpected finding, this study (2) also supports the important and often forgotten notion that success in science is not only to discover new things, but also to better understand old observations in new ways.

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