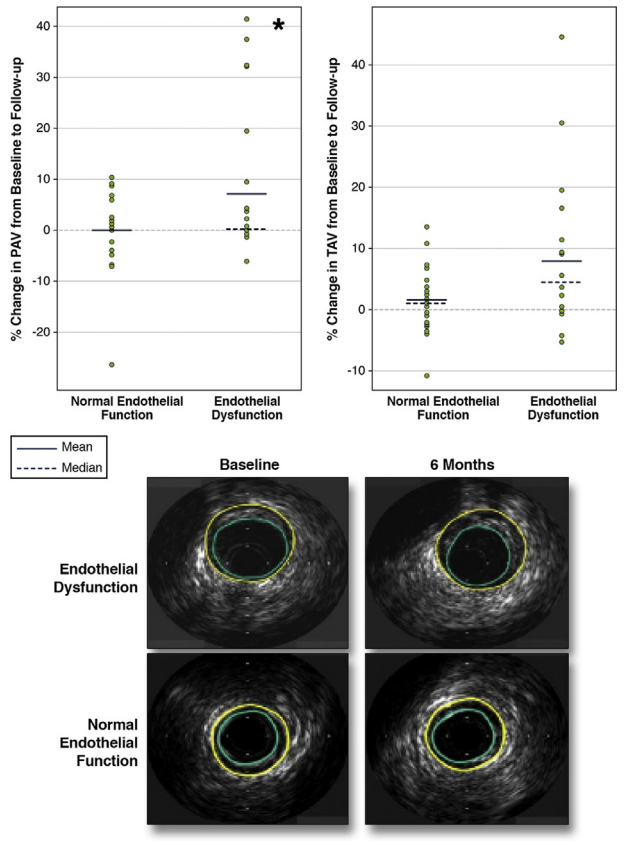

Figure 1. Comparison of Intraindividual % Change of Normalized PAV and TAV Between the Segments With Endothelial Dysfunction and Those With Normal Endothelial Function

The % change of normalized percent atheroma volume (PAV) is shown in the **upper left panel** and of total atheroma volume (TAV) in the **upper right panel**. The comparison is between segments with endothelial dysfunction and those with normal endothelial function. Representative examples of intravascular ultrasound (IVUS) findings are shown in the **lower panel**. Segments with endothelial dysfunction showed greater progression in PAV (*$p < 0.05$) and TAV ($p = 0.065$) than segments with normal endothelial function from the same subject. IVUS demonstrates the progression of disease-only segments with endothelial dysfunction (lumen traced in **green**, external elastic membrane in **yellow**).

70% plaque burden and IVUS-VH–derived thin-capped fibroatheroma are more likely associated with the progression of atherosclerosis and recurrent coronary events (4). Thus, the current study extends these previous observations and demonstrates that coronary artery segments with relatively small plaque burden, but evidence of endothelial dysfunction, show faster plaque progression over a relatively short period of time than segments with similar plaque burden at baseline, but normal endothelial function. Thus, segments with endothelial dysfunction may represent the earliest identifiable site with underlying vascular injury, but abnormal repair prone to accelerated plaque progression and complications.

The mechanism for plaque progression at the segments with endothelial dysfunction may be multifactorial, but the reduced activity of endothelium-dependent vasodilators, particularly nitric oxide activity, an increased activity of vasoconstrictors with mitogenic activity, and altered anti-inflammatory and anticoagulant properties of the endothelium likely contribute to accelerated plaque progression.

The lack of correlation between the severity of endothelial dysfunction and plaque progression suggests that plaque progression is independent of changes in the degree of coronary endothelial reactivity.

In conclusion, atherosclerosis is a diffuse and systemic disease with focal complications. The ability of in vivo identification of coronary artery segments with propensity for plaque vulnerability that are at risk for plaque progression and the development of cardiovascular events may potentially have implications for future site-specific therapy beyond the systemic therapy for patients in early coronary atherosclerosis.

Mario Gössl, MD, Myeong-Ho Yoon, MD, Byoung-Jwoo Choi, MD, Charanjit Rihal, MD, Jonella M. Tilford, Martin Reriani, MD, Rajiv Gulati, MD, Guri Sandhu, MD, Erik Eeckhout, MD, Ryan Lennon, MS, Lilach O. Lerman, MD, PhD, Amir Lerman, MD*

*Mayo Clinic, 200 First Street SW Rochester, Minnesota 55902. *E-mail: Lerman.Amir@mayo.edu*

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Definitions of Outcome, Response and *Effect* in Imaging Research to Avoid Confusion

"Outcome," "response," and "effect" are not the same. Unfortunately, these terms are commonly used interchangeably in imaging research, which can lead to problems with study design and misinterpretation of results. We propose and illustrate simple definitions to allow these fundamentally different concepts to be distinguished for clear communication between authors and readers of scientific papers.

OUTCOME

"Outcome" is a measured value, which can be a state of health or an event, subsequent to an intervention. Outcome data is easy to

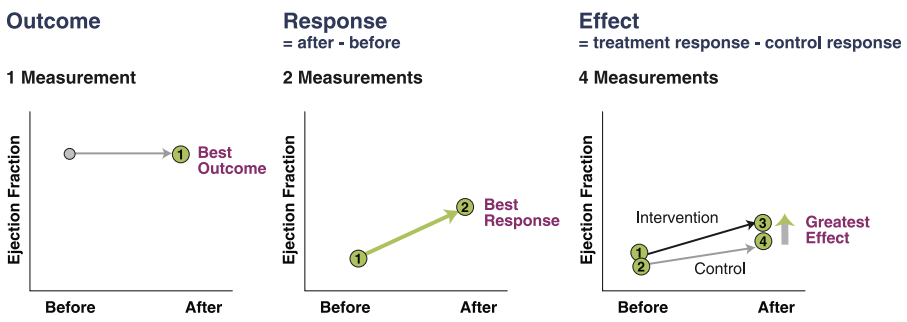

Figure 1. Why "Outcome," "Response," and "Effect" are Distinct

"Outcome" is a measured value subsequent to an intervention. "Response" is the change in a measured variable from before to after an intervention. "Effect" is the difference in response between an intervention group and a control group.

obtain, as it requires only 1 measurement and no knowledge of measurements made prior to intervention. It can be a useful and valid method for assessing whether health care needs have been met or not.

RESPONSE

"Response" is the change in a measured variable from before to after an intervention. For example, it could be the change in ejection fraction after biventricular pacemaker insertion. Avoiding bias is challenging, because clinical staff know patient characteristics, whether the patient has had an intervention, and what the previous measurements have been. Response is an unreliable and often deceptive metric because, without a control group, it cannot distinguish among background variation, the natural history of disease, and the effects of an intervention.

EFFECT

The "effect" is the difference in response between patients that have undergone an intervention compared with the response of a control group and thus requires 4 measurements to be compared. This is more complex but is the key metric that should dominate clinical decisions about therapeutic interventions because it distinguishes the effect of an intervention from the natural history of disease. "Efficacy," "effectiveness," "advantage," "net benefit," or "net harm" are other terms that can be used instead of "effect."

OUTCOME, RESPONSE, AND EFFECT ARE NOT INTERCHANGEABLE

If 3 patient groups are undergoing an identical intervention, it is possible that the group that has the best outcome, the group that has the best response, and the group that receives the greatest effect are all different (Fig. 1).

Consider a hypothetical example of Agent X, which is known to dramatically increase left ventricular ejection fraction (LVEF), but only in patients with dilated cardiomyopathy and low LVEF. Imagine it being examined in 3 groups:

- Group 1: testing in healthy subjects to establish safety;
- Group 2: a first-in-man open-label study at the center that invented Agent X, in the early minutes after successful primary angioplasty for myocardial infarction; and
- Group 3: a double-blind placebo-controlled trial in patients with dilated cardiomyopathy and low LVEF.

Group 1 will have the best "outcome," because these subjects have the highest baseline LVEF. Agent X does not change a normal LVEF. There is no response and no effect. Group 2 may have the best "response" because with prompt revascularization myocardial function will recover substantially in many patients, independent of Agent X. Group 3 may have the greatest increase in LVEF attributable to the intervention so it will have received the greatest "effect."

If our community judged clinical usefulness on outcome or response, Agent X might be considered inappropriate for Group 3, even though they are the only ones who truly benefitted at all.

To illustrate this concept, look at studies of cardiac resynchronization therapy (CRT) by searching for "echocardiography and CRT" in Europe PubMed Central. Frequently, trials use the terms "outcome," "response," and "effect" (or "benefit") without a clear separation in meaning (Fig. 2) and in some cases interchangeably.

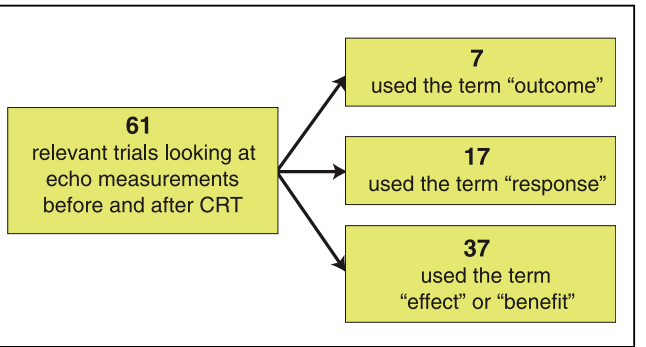

Figure 2. An Example That Illustrates How Commonly These Terms are Used to Describe the Same Concept

We examined 61 studies of cardiac resynchronization therapy (CRT). There was inconsistency in the use of the terms "outcome," "response," and "effect."

One pitfall of reporting response is the phenomenon of "regression to the mean." If enrollment requires a measurement below a certain threshold, using a test with an element of variability, such as LVEF, a measurement taken on 1 particular day might be lower than the patients' true average value. When the test is repeated (after the intervention), the measurement is likely to have risen closer to the patients' true average. This may give the false impression of a therapeutic improvement. Unless there is a control group for comparison, a reader may be misled into thinking that an intervention is effective. Describing an intervention as "effective" should be reserved for the findings of randomized controlled trials where there is a significant difference between the intervention and control groups.

The terms "outcome," "response," and "effect" are sometimes used interchangeably in imaging research. We suggest simple definitions to facilitate clear communication and avoid misinterpretation of findings and even of study design.

Sonia Bouri, MBBS, BSc,* Zachary I. Whinnett, PhD, Graham D. Cole, MA, MB, BChir, Charlotte H. Manisty, MBBS, PhD, John G. Cleland, MD, PhD, Darrel P. Francis, MA

*Dr. Sonia Bouri, International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, 59-61 North Wharf Road, London W2 1LA, United Kingdom. *E-mail: soniabouri@nhs.net*

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Qualitative Characterization of Adipose Tissue by MDCT

We read with great interest the paper by Rosenquist et al. (1) published recently in *iJACC*. The analysis performed on a large cohort drawn from the Framingham Heart Study implies that lower multidetector computed tomography (MDCT) attenuation of subcutaneous adipose tissue and visceral adipose tissue is associated with an adverse cardiometabolic risk profile. We would like to reflect on 2 aspects of the published data.

First, although imaging of adipose tissue by MDCT offers relatively high resolution and reproducibility and has increasingly been used as a research tool, the methodology of computed tomography fat volume calculations has never been validated. Measurements are based on an arbitrary attenuation range (Hounsfield units), which is not set uniformly across the literature. Such attenuation-based identification may lead to the parts of adipose tissue with the lowest and highest attenuation being left unaccounted for. Furthermore, attenuation relies substantially on computed tomography scan parameters, especially tube voltage (kV), and also on patients' characteristics. Tube voltage is often set differently for lean and obese patients. All of these factors may lead to a systematic bias in interpretation of a study such as that by Rosenquist et al. (1). Scan parameters applied in the reported cohort were not mentioned in the paper.

Second, we know from basic research studies that adipose tissue may display either an unfavorable or a favorable metabolic profile (endocrine and paracrine) depending on its location and metabolic status (2). As an example, epicardial adipose tissue in patients with coronary artery disease as opposed to patients without this disease showed intense leukocyte infiltration, thickened interlobular septa, and increased neovascularization (3). All of these elements are more radiodense than lipid-laden adipocytes and thus may lead to higher, rather than lower, MDCT attenuation of adipose tissue with a proinflammatory and proatherosclerotic metabolic profile. Results of our clinical study corroborate this hypothesis (4). Furthermore, as noted by Rosenquist et al. (1), lower attenuation of subcutaneous adipose tissue and visceral adipose tissue was correlated with fat volume because larger, lipid-laden adipocytes are less attenuating. In such circumstances, in a retrospective, cross-sectional study, it may be difficult to distinguish the effects of fat volume from those of its attenuation. Thus, it would be interesting to see how the attenuation correlated with cardiometabolic risk factors within subgroups with similar fat volumes.

To summarize, the study by Rosenquist et al. (1) adds significantly to the growing body of evidence on the research and clinical role of MDCT-derived characterization of adipose tissue. However, further research efforts to eliminate the aforementioned limitations are warranted. Longitudinal designs, histopathology references, methodological improvements, standardization of MDCT fat measurements, and prospective methods of accounting for the established confounding factors in adipose tissue attenuation and volume measurements should be clarified to further develop this new, fascinating area of research.

Radoslaw Pracon, MD, PhD,* Mariusz Kruk, MD, PhD, Marcin Demkow, MD, PhD

*Department of Coronary and Structural Heart Diseases, 42 Alpejska Street, Institute of Cardiology, 04-628 Warsaw, Poland. *E-mail: radekpracon@yahoo.pl*

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Myocardial Extracellular Volume Measurement by Cardiac Magnetic Resonance

Measuring myocardial extracellular volume (ECV) with cardiovascular magnetic resonance is achieving increasing importance because it allows quantification of diffuse fibrosis not detectable with conventional late gadolinium enhancement techniques. However, the conditio sine qua