As an alternative to ratio calculation, we can also explore whether the linear difference between thickness measurements is machine invariant. Consider the difference between the thicknesses at the different time points:

\[ \Delta d_\alpha = d_{\alpha 2} - d_{\alpha 1} = (c_2 - a_2) - (c_1 - a_1) = (c_2 - c_1) - (a_2 - a_1) \]

and, similarly,

\[ \Delta d_\beta = d_{\beta 2} - d_{\beta 1} = (c_2 - b_2) - (c_1 - b_1) = (c_2 - c_1) - (b_2 - b_1). \]

The condition for machine invariance here is that

\[ \Delta d_\alpha - \Delta d_\beta = 0. \]

From this calculation, we have

\[ (b_2 - b_1) - (a_2 - a_1) = 0. \]

which is the case only if the reference planes do not change position during the time interval or if the difference between the two planes is negligibly small.

It may be that for some diseases, such as diabetic retinopathy and other retinal vascular diseases, that only the inner retinal layer moves and the reference planes (e.g., the tips of the outer segment or the first bright RPE reflection) do not move, in which case the linear difference between measurements will be machine invariant (as \((b_2 - b_1)\) is zero and \((a_2 - a_1)\) is zero).

However, in florid cystoid macular edema, where the photoreceptor layer itself detaches from the RPE or where the position of the RPE layer moves (e.g., RPE detachment reduces after intravitreal ranibizumab), then the linear difference between different machines will not be invariant.

In summary, retinal thicknesses derived from OCT measurements are interval data. There is no natural zero, and the numerical value of the thickness always depends on the choice of reference plane. The ratio of two thickness measurements made at different time intervals and the logarithm of this ratio varies from machine to machine. The linear difference between thicknesses at these different times may be machine independent, but only if the position of the reference plane remains unchanged with the passage of time.

We therefore warn the retinal community against performing studies in which different OCT machines are used and ratios of thicknesses are calculated and treated as comparable. Such comparisons would introduce errors in the data that are collected. We hope that our analysis explains this concern.

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Citation: *Invest Ophthalmol Vis Sci.* 2012;53:853–854. doi:10.1167/iovs.12-9445

**Author Response: Retinal Thickness Measurement in OCT**

The authors thank Davies and Parvizi for their thoughtful comments about our paper published in the November 2011 issue. We are grateful for the opportunity to respond to their comments.

We believe that each of the approaches is correct; however, it is critical to understand the meaning, limitations, and potential biases of using a difference in the logarithmically transformed optical coherence tomography (OCT) data. As shown mathematically in our paper, a given ratio change (e.g., a change from 320 to 400 μm or 400 to 500 μm) yields a fixed change in the logOCT (in these examples, \(-0.1 = \log_{10}(320/400) = \log_{10}(400/500)\) regardless of the choice of a normalizing baseline (e.g., 200 for logOCT or 250 for SD-logOCT).

We acknowledge that these changes in the logOCT value do not represent the same absolute change in retinal thickness across machines. We also recognize that if the same patient were to be measured on two different devices, then two different logOCT measurements would be obtained, as we discussed in our paper. However, we can still envision situations in which this method would be useful and advantageous. For example, if a study were designed to determine the number of patients who achieve a 20% reduction in retinal thickness (about a \(-0.1 \ logOCT \ change \ as \ illustrated \ above\)) and if the study outcome were based on repeated measures of each patient on their same OCT device, then the change in logOCT would indeed be invariant to the machine’s reference plane. As illustrated by Davies and Parvizi, a machine that includes additional retinal layers will measure greater retinal thicknesses on average and is therefore at a relative disadvantage in such a study because greater absolute changes would be necessary to achieve a given percentage of reduction. However, if a cohort of patients were described as a single whole or if there were no imbalance in the variety of machines used between the groups compared, then it would be reasonable to use multiple devices in a single study. Because randomization should balance the measurement devices used across the interventions, such an approach would be reasonable in a randomized clinical trial. While these same considerations would also make it reasonable to use the absolute change in retinal thickness across devices in certain situations, we...
believe logOCT’s other advantages make it a better measure of meaningful clinical change.

Furthermore, in many cases the bias would be expected to be negligible, even across devices. For example, the outer retinal boundary for the 3D OCT-1000 device (Topcon, Tokyo, Japan) is at the photoreceptor outer segments. The outer retinal reference plane for the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) and RTVue-100 (Optovue, Fremont, CA) devices includes the photoreceptor outer segment tips, measuring slightly closer to the retinal pigment epithelium. Assuming that there is no pathology occurring between the devices’ reference planes, the differences between the 3D OCT-1000 and the other two devices would be approximately 20 μm. The differences between the Cirrus HD-OCT and the RTVue-100 would be expected to differ by no more than 5 to 10 μm, because their reference planes are the same. For example, in our longitudinal study of 34 patients, we observed a mean maximum central retinal thickness of 495 μm and a mean minimum of 315 μm, resulting in a mean change of −180 μm during the study. The result was equivalent to a mean change in logOCT of −0.192 units. We calculated that if these same patients had been measured on a different machine that increased the baseline thickness consistently by 20 μm, we would have instead found a mean change of −0.182 units, a bias of 0.01 logOCT units (equivalent to a −2% change in the retinal thickness). We suggest that this bias is negligible and would most likely be overwhelmed by other random and nonrandom variations that would occur in the course of a study. In addition, most clinical trials use reading centers that can manually set the reference plane of the OCT and therefore “standardize” the measurements of retinal thickness.

Finally, we agree that it is important that all devices used in a given study include all retinal layers that are affected by the pathology under study. Otherwise, changes in outer layers included by one device but not by another could result in unfair comparisons. In uveitis, edema can occur in many retinal layers, but most often occurs within the neurosensory retina and, in particular, the outer plexiform layer. Prior studies assessing OCT features of uveitic macular edema have identified diffuse macular edema and cystoid macular edema as the predominant uveitis subtypes with serous retinal detachment without retinal thickening, comprising a minority of cases. Because the reference planes for the various spectral-domain OCT machines are typically at the photoreceptor layer, outside of where changes typically occur in uveitis, the problems highlighted by Davies and Parvizi regarding changes occurring between the reference planes are not likely to result in meaningful differences in uveitis research; but we concur that this consideration is an important one for the study of other diseases (e.g., age-related macular degeneration).

In conclusion, we appreciate the concerns of Davies and Parvizi and re-emphasize their call for caution when considering using multiple devices in the same study. However, we do believe that logarithmic transformation of OCT data provides an advantageous way to evaluate clinically meaningful changes across a study population, provided that those designing and analyzing the study have a firm understanding of the limitations of such approaches. Nevertheless, we also agree that it remains ideal to use consistent equipment across all study sites to avoid even the potential for such biases and to allow data to be compared directly with greater ease.

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doi:10.1167/iovs.12-9527