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## Olive Oil and Ischemic Reactive Hyperemia in Hypercholesterolemic Patients

I read with interest the study by Ruano et al. (1) reporting on the protective effect of olive oil on cardiovascular markers. In their study, the investigators demonstrate that olive oil reduces plasma evidence of oxidative stress, increases nitric oxide (NO) production, and limits the blunting in cutaneous reactive hyperemia observed in hypercholesterolemic subjects. The researchers conclude that "olive oil [. . .] improves endothelium-dependent microvascular vasodilatation." Whereas the evidence of the beneficial effect of olive oil on plasma markers is convincing, the interpretation of laser Doppler data appears somewhat simplistic and worthy of further discussion.

First, the evidence that ischemic reactive hyperemia can be used as an index of endothelial function is very inconclusive. Recently, Binggeli et al. (2) showed that cutaneous reactive hyperemia is absolutely NO-independent and only marginally (approximately 30%) influenced by release of cyclooxygenase products. Of importance, Rossi et al. (3) convincingly showed that the influence of the endothelium accounts only for approximately one-quarter of the forces regulating resting vasomotion, and that this percentage does not increase after ischemia. Moreover, hundreds of studies employing the brachial artery flow-mediated dilation method have shown that reactive hyperemia is preserved in a number of conditions associated with impaired endothelial function.

With this evidence, one should be very careful in attributing a blunted reactive hyperemia to dysfunction of any of the factors determining vascular tone (e.g., metabolic vasodilation, myogenic tone, endothelial function, and others). The investigators quote the study by Vuilleumier et al. (4) However, that study shows an association between cutaneous reactive hyperemia and cardiovascular risk factors, and it provides no mechanistic information regarding a causal relationship between laser Doppler parameters and release of vasoactive endothelium-derived autacoids. There is no discussion that microvascular vasomotion (including its endothelial component) is of critical importance to vascular homeostasis and that laser Doppler indexes can be reliably used as surrogate markers of cardiovascular health. However, there is a worrying trend toward identification of "endothelial" and "microvascular" vasomotor control. It should be emphasized that these terms are not synonyms, and that they should not be used interchangeably.

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## REPLY

We want to convey our gratitude to Drs. Gori, Giugliano, and Esposito for their interest in our work, which has caused us to reflect on the most relevant data in our study (1). Both letters emphasize a series of points with which we generally agree. With respect to the issues advanced by Drs. Giugliano and Esposito, a number of studies have investigated the effects of acute ingestion of olive oil using various amounts of this foodstuff that have usually ranged from 25 ml (2), 44 ml (3), 50 ml (4,5) to 65 ml (6), and 108 ml (7). After administering the lowest quantity mentioned here, Weinbrenner et al. (2) did not observe any significant alterations in either postprandial lipemia or oxidation markers. In our study, we decided to employ a volume of 40 ml, an intermediate value among those mentioned above, and one that does not exceed the mean daily consumption in Mediterranean countries. This design led us to register an increase in the concentration of plasma triglycerides, with a peak level occurring 2 h after the ingestion of both breakfasts. Moreover, unlike the situation in the study of Bonanome et al. (7), none of the participants displayed intolerance or rejection in the course of ingestion. Our choice of volume was based on our interest in studying the effects of an ingestion of olive oil approximately equal to the amount utilized in tests of postprandial lipemia, which tend to be about 0.5 to 1.0 g/kg body weight. We believe it could be interesting now to look for a potential threshold for the ingestion of phenolic compounds, employing different volumes or types of virgin olive oil, with the aim of arriving at a breakfast that would be easy to consume while guaranteeing the potential beneficial effect.

The comments of Dr. Gori also merit particular attention; his letter demonstrates a profound understanding of the methods involved in the study of endothelial function. The most interesting finding of our study was the rise in the values of ischemic-reactive hyperemia (IRH) following the ingestion of olive oil with an elevated content of phenols. We employ the term IRH rather than "microvascular endothelial function" as used by other investigators, because of the uncertainty arising from the lack of exact knowledge of the relationship between this parameter and endothelial function, although previous studies claim to have established such a relationship (8).

Conversely, the correlation between the plasma concentration of nitrates and nitrites and IRH was high ( $R^2 = 0.588$ ), which suggests that the availability of nitric oxide (NO), proceeding from the endothelium, plays an important role in the observed response of IRH. At any rate, Dr. Gori's discussion is of great interest, and