Reviewer's report

Title: Impairment of Microvascular Coronary Flow Reserve- The Materialisation of the Ghost

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Reviewer: Paolo Voci

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The editorial by Dimitrov et al focuses on an interesting aspect of modern cardiovascular physiology, but unfortunately is contradictory and confusing.

The authors start claiming that CFR is a useful index to investigate both severity of coronary epicardial stenosis and dysfunction of coronary microcirculation but they also write that CFR is reduced below 2.0, corresponding to the same cut-off point for severe epicardial artery stenosis in a number of diseases (hypertension, diabetes, hypercholesterolemia, syndrome X, hypertrophic and dilated cardiomyopathies). How such an index can be useful to detect epicardial stenosis if there is so much overlap with diseases/conditions characterized by microvascular dysfunction? The authors should also recognize that syndrome X is characterized by a supernormal CFR and systolic function at stress, in hypercholesterolemia the reduction of CFR if ever present, is minimal, and that in hypertension and aortic valve disease CFR may be reduced only because part of the reserve is already burned at rest, due to the increased metabolic demand.

The Authors mention with emphasis the work by Hoffman (ref#2) who suggest that CFR of 2.5 or even 3 are potentially damaging to the subendocardium. How is it possible that an increase in flow of up to 3-fold may be damaging? Of note, the great majority of middle-age people have a CFR around 3 (see page 5): are we all at risk of subendocardial damage? In contradiction with this statement is the finding reported in ref 8 and 9 that transplanted hearts have an early CFR of 5.1 despite all what their subendocardium has suffered during agony of the donor, cold-preservation and then transplantation. Of note, 5.1 is the CFR of athletes.

The authors state on page 5 that Positive exercise myocardial scintigraphy, primarily considered as false positive in relation to angiographically normal coronary vessels, may frequently turn out to be true positive when control intracoronary ultrasound reveals vascular lesions (18); in this setting, CFR is a fairly good predictor of soft lesions, not visualized by coronary angiography. This sentence should be deleted.

Page 6: in some pediatric patients with hypertrophic cardiomyopathy, CfR was <1 (since non-hypertrophic free wall steals blood flow from hypertrophied septum after vasodilator infusion). However, there are no angiographic collateral to support such a huge steal; in addition, a CFR<1 corresponds to coronary subocclusion, with severe ischemic signs and symptoms.

The reported experience by Rigo is based on a drug (dipyridamole) which does not necessarily produce maximal microvascular dialation, and with an inadequate ultrasound equipment.

In the reference list the Authors failed to mention the most important papers published on coronary flow reserve by other groups mainly in Italy and Japan.

What next?: Reject because scientifically unsound

Level of interest: Too insignificant to warrant publication in any journal
Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I received reimbursement from siemens-acuson