

The Past Present and the Future of Coronary Arterial Lesions with a Non-Ischemic Fractional Flow Reserve (FFR 0.80 and Above)

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Editorial

Coronary artery disease is major cause of morbidity and mortality [1,2]; it accounts for 1% of all visits to the general practitioner [3,4], 5% of all emergency department visits and 40% of all admissions [5]. In 2010 CVD accounted for 31.9% off all deaths [6]. In the same time period coronary heart disease (CHD) caused approximately 1 of every 6 deaths in the United States [6]. An estimated 620000 Americans have a new coronary attack every year and 295000 will have a recurrent attack each year [6]. An additional 150000 silent first myocardial infarctions occur each year [6]. 1 American has a coronary event every 34 s and an American will die from CHD every 1 min 23 s [6].

The first selective coronary angiogram was performed when Dr F. Mason Sones Jr. when he inadvertently engaged the right coronary artery on October 30, 1958 [7]. Since then we have come a long way riding on the shoulder of giants such as Melvin Judkins and others [8]. We soon realized that coronary angiography alone cannot determine the physiological significance of stenosis.

Pijlis et al. validated fractional flow reserve (FFR) by studying 45 patients with an intermediate coronary stenosis with bicycle exercise testing, dobutamine echocardiography, thallium scintigraphy and quantitative coronary angiography. The results on the above tests were compared with the measured fractional flow reserve [9]. The sensitivity, specificity, positive and negative predictive values of a FFR value of 0.75 were determined to be 88%, 100%, 100% and 88% respectively. FFR value of less than 0.75 was associated with myocardial ischemia and a value of more than 0.80 was non ischemic, FFR values in between were considered borderline [10].

Outcome studies that followed determined the natural history of borderline and non-ischemic lesions. Studies on borderline lesions showed that such lesions have a poor prognosis in the absence of revascularization [11-13]. The current FFR threshold for intervention is 0.80 based on the results from FAME [14,15]. Finally many well-known trials demonstrated that deferred lesions have an excellent long term prognosis [16-18]. However recent trials questioned the wisdom of deferring all lesions with an FFR above 0.80 [19-21].

The answer to these discrepancies probably lies in understanding the role of coronary microvascular resistance. An exhaustive discussion of invasive assessment of coronary physiology is beyond the scope of the current discussion, briefly in a normal vessel FFR and coronary flow reserve (CFR) should be normal and index of microcirculatory resistance (IMR) should be low [22]. Isolated epicardial stenosis leads to a lowering of FFR, CFR and IMR [22]. When diffuse atherosclerotic narrowing is superimposed on a focal epicardial stenosis the FFR can be falsely normal however the IMR and CFR will both be low [22]. When focal stenosis and microcirculatory

dysfunction coexist both FFR and IMR will be elevated but CFR will be low [22]. Hence FFR can be normal inspite of a significant epicardial stenosis [22]. A high IMR has been shown to play an important role in heart failure [23,24], in smokers [25] and in those with acute coronary syndrome [26,27].

Although IMR is the most important factor contributing to the discrepancy it is possible that there are at least 2 other factors that may play a role. The first is the ability of the myocardium to adapt to ischemia [28,29]. It makes intuitive sense that a lesser degree of flow reduction may suffice to produce ischemia in the presence of pre-existing myocardial pathology that limits the ability to adapt to ischemia. Finally the acuity of onset of the ischemic insult is also important. It is likely that a permutation and combination of these three factors play a role in conditions such as heart failure [23,24], in acute coronary syndromes [26,27], in those with a H/O previous MI, in patients with COPD [25]. In summary the discrepancy between a non-ischemic FFR and adverse clinical outcomes can be explained by the presence of a high microcirculatory resistance, other factors that probably play a role include the ability or lack thereof of the myocardium to adapt to ischemia and the acuity of the ischemic insult.

These factors should be addressed in future trials that study outcomes in non-ischemic coronary lesions. If it is proven that such factors play an important role, it will lead to a paradigm shift in the way we approach coronary physiology in the cardiac catheterization laboratory.

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