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The ischaemic constellation: an alternative to the ischaemic cascade—implications for the validation of new ischaemic tests

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ABSTRACT

The ischaemic cascade is the concept that progressive myocardial oxygen supply–demand mismatch causes a consistent sequence of events, starting with metabolic alterations and followed sequentially by myocardial perfusion abnormalities, wall motion abnormalities, ECG changes, and angina. This concept would suggest that investigations that detect expressions of ischaemia earlier in the cascade should be more sensitive tests of ischaemia than those that detect expressions appearing later in the cascade. However, careful review of the studies on which the ischaemic cascade is based suggests that the ischaemic cascade concept may be less well supported by the literature than assumed. In this review we explore this, discuss an alternative method for conceptualising ischaemia, and discuss the potential implications of this new approach to clinical studies and clinical practice.

INTRODUCTION

The ischaemic cascade was initially described over 20 years previously,[1] based on experiments in animals[2–9] and humans,[10–20] and refers to a temporal sequence of pathophysiological events that occur with increasing myocardial oxygen supply–demand imbalance. The ischaemic cascade has been described as occurring in the following sequence: metabolic alterations, inducible changes of perfusion, diastolic dysfunction, regional systolic wall motion dysfunction, ischaemic ECG changes and finally angina.[1]

A cascade is a sequence of events, each of which triggers the next. Since causation is difficult to demonstrate directly, instead progression is demonstrated and causation inferred. To create progressively more intense ischaemia within an individual animal, so that the sequence of emergence of elements of the cascade can be identified, three broad approaches are possible (figure 1):
▶ Progressively tighter stenosis, with workload kept constant and measured at steady state.
▶ Progressive passage of time after a fixed acute occlusion, with workload kept constant.
▶ Progressively increasing workload, with stenosis kept constant and measured at steady state.

Assembling data from experiments that use different possibilities from the three ways of spreading ischaemia intensity on a spectrum relies on the assumption that the three different meanings of increasing ischaemia are equivalent. If the ischaemic cascade model is accurate, the order of events should be the same in all three. For example, it might be metabolic alterations first, followed sequentially by myocardial perfusion abnormalities, wall motion abnormalities, ECG changes and angina. If this assumption is not correct then we should be much more thoughtful when displaying illustrations of the process of ischaemia.

Metabolic alterations consist of the conversion from aerobic to anaerobic myocardial cell metabolism, thus producing biochemical changes of lactate, and cellular polarity. At a single-cell level a cascade is feasible, however cellular events will not occur synchronously in all cells beyond a stenosis. It is the later stages of the ischaemic cascade concept that are of clinical interest, but these can be subject to confounding effects of concomitant medications and varying degrees of coronary disease.

If the ischaemic cascade is not as solid a sequence as is often portrayed, this article discusses how the process of ischaemia could be conceptualised, the implications this has on the development of new tests of ischaemia and the implications for clinical practice.

Some clinicians and scientists may have already rejected the ischaemic cascade for not being true; for them, our paper is attacking a 'straw man'. Unfortunately however, figures and slides are commonly shown[21–24]

Figure 1 Three different 'x axes' along which to rank states for ischaemia. The underlying hypothesis behind the ischaemic cascade is that the order of development of the various manifestations of ischaemia is the same for all three main ways of producing the ischaemia phenomenon. One approach is to ligate a coronary artery and monitor carefully in the ensuing seconds, with the temporal sequence of events showing the cascade sequence. A second is to progressively increase stenosis. A third is to progressively increase workload. If these three methods of inducing progressively more severe ischaemia produce manifestations in conflicting sequences, the ischaemic cascade concept is imperilled.

and clinical studies (that use a single 'gold standard' for ischaemia) continue to assume that the cascade is true. This implies that rejection of the ischaemic cascade is not yet universal, and therefore our paper may be a useful enumeration of information.

METHODS

Literature search was performed in accordance to the PRISMA statement.[25] Studies were identified by searching Medline (1946 to February 2015) and Embase (1974 to February 2015), using the search term 'ischaemic cascade' (both English and American spellings). The search was restricted to English language and case reports were excluded. Reference lists of the retrieved articles (including reviews and editorials) were hand-searched for additional publications. The methodological validity of each included study was assessed using criteria for minimisation of bias, including definition and measurement of outcome, blinding, presence of a control group, and sample size (figure 2).

FOUNDATIONS OF THE ISCHAEMIC CASCADE

The original paper,[1] describing the ischaemic cascade, was based on human studies[10–20] (table 1). The methods used to induce supply–demand mismatch were as follows: (1) coronary artery balloon occlusion,[10–12] (2) atrial pacing tachycardia,[13–15] (3) exercise testing[16–19] and (4) spontaneous angina,[20] that is, episodes of myocardial ischaemia at rest (either spontaneous or ergovine induced) in patients with Prinzmetal's angina.

It is far from clear whether the events after abrupt occlusion of a coronary artery, coronary vasospasm, or increased myocardial workload, match what happens in

incremental ischaemia with chronic coronary artery stenosis. Nonetheless, these studies[10–20] show that angina and/or ST segment depression does not consistently accompany ischaemia. More importantly, they show that when angina and/or ST segment depression do occur, their temporal relationship with other elements of the ischaemic cascade is not always what would be expected if the cascade is correct. Studies that support the sequence of events in the ischaemic cascade are summarised in table 1.[10 11 13–15 17 19 20 26–31] Table 2 summarises studies that contradict the sequence of events described in the ischaemic cascade.[12 16 18 32–34]
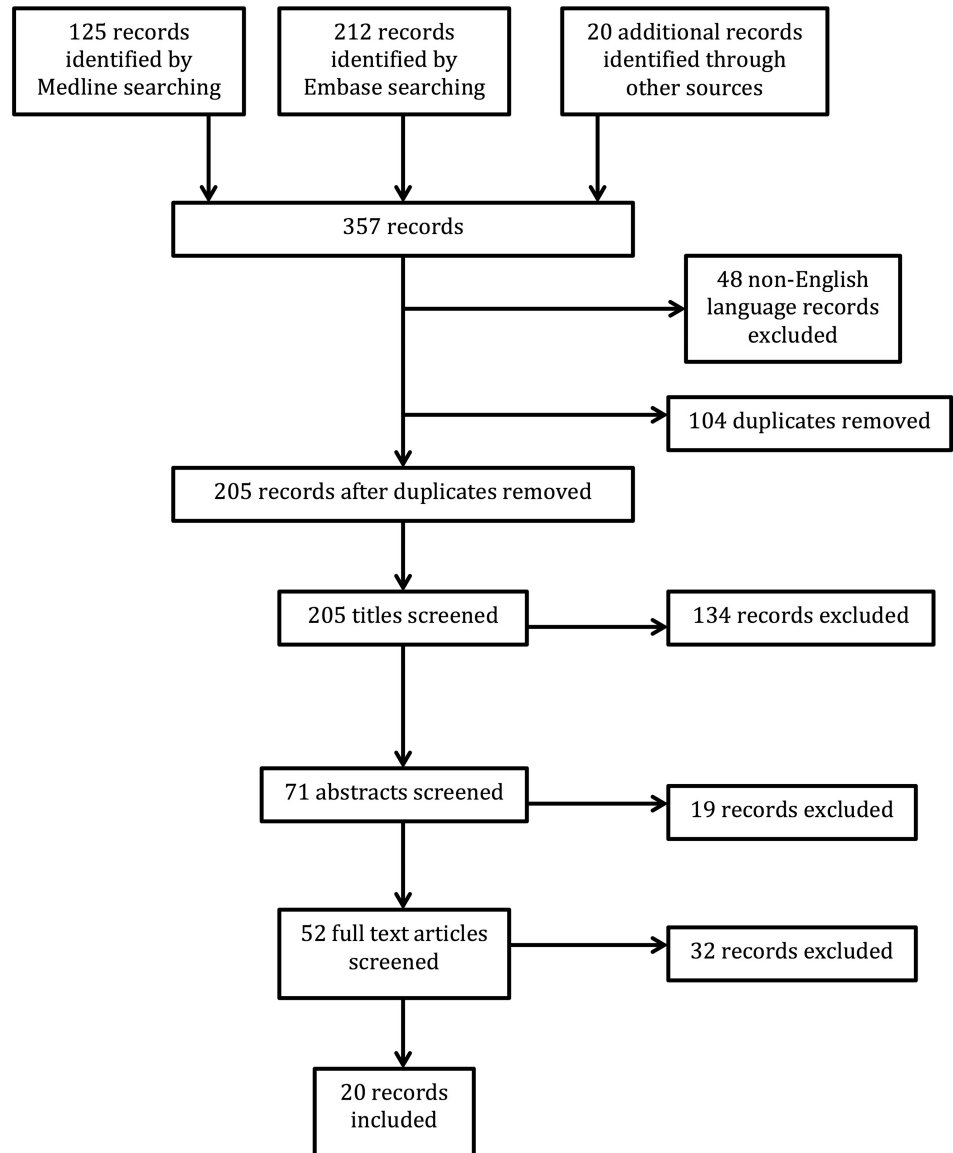
SEQUENCE MISMATCHES

The term 'cascade' is a reference to a sequence of events, each triggering the next. It is used to describe waterfalls, where what falls to one level becomes available to fall to the next level down (figure 3). If, however, events are observed to occur out of sequence, then impression of causality (or at least ordering) conveyed by the term 'cascade' may not be secure.

Close inspection and comparison of the results of different studies, included in the original ischaemic cascade concept paper,[1] suggests that the sequence of events described is not conserved across patients (table 2). For instance, one study[18] found that when diastolic dysfunction was measured using pulmonary artery pressure during exercise, the onset of ST segment depression occurred before diastolic dysfunction in 38% of episodes, was simultaneous with it in 38% of episodes, and followed it in only 24% of episodes.

In another study of patients with angina who underwent continuous ECG and echocardiographic monitoring

Figure 2 Flow diagram of literature search.

In a further study of 707 consecutive patients screened after dobutamine or bicycle ergometer stress echocardiography, only 12% of patients followed the classical ischaemic cascade.[32] Only 30% had regional perfusion defects prior to the onset of abnormal wall motion, whereas 22% had perfusion defects seen during or after the onset of abnormal wall motion.[32] These findings and those of others[33][34] contradict the sequence of events described in the ischaemic cascade.

THE ISCHAEMIC CONSTELLATION

In light of the data conflicting with the concept of any single ischaemic cascade, perhaps the concept of a single sequence of stepwise causality needs to be re-evaluated.

during dipyridamole infusion, the sequence of ischaemic events observed were markedly variable.[33] Of those patients who developed echocardiographic and ECG changes/angina, only about half exhibited regional wall motion abnormalities first, while the remaining half exhibited ECG changes and or angina first.

In a true cascade, where each event leads to the next in succession, there is no doubt regarding the causal sequence of events. For example, in the complement cascade of the immune system each stage is necessary for the next to occur.

In contrast to a cascade model of ischaemia, we propose that a more befitting model of myocardial ischaemia may be the 'ischaemic constellation'; a collection of observations that may occur in a variety of sequences. An ischaemic constellation would include all clinical aspects of the cascade, including angina, myocardial perfusion abnormalities, ST segment depression and wall motion abnormalities, without the artificial prerequisite of a need to occur in a particular preordained order. Such a constellation would explain the similar rate of positivity of tests of ischaemia and their variable ordering of apparent sensitivity in different patients.[35]

Conceptualising ischaemia in this way would perhaps be more consistent with clinical practice. Currently, clinicians who would otherwise be restricted by the concept

Table 1 Summary of human studies that support the sequence of events in the ischaemic cascade

Study	Sample size	Ischaemic state	Blinded study
Sestito et al[30]	30	Dipyridamole stress echocardiography	Not reported
Kyrzopoulos et al[31]	148	Dobutamine stress echocardiography	Not reported
Heller et al[29]	19	Exercise testing	Yes
Williams et al[28]	104	Bicycle ergometer stress echocardiography	Not reported
Nixdorff et al[27]	16	Bicycle ergometer stress echocardiography	Yes
Hyodo et al[26]	53	Dobutamine stress echocardiography	Yes
Alam et al[10]	12	Coronary artery occlusion	No
Hauser et al[11]	18	Coronary artery occlusion	Not reported
McLaurin et al[13]	15	Rapid atrial pacing	Not reported
Iskandrian et al[14]	12	Rapid atrial pacing	Not reported
Aroesty et al[15]	22	Rapid atrial pacing	Not reported
Reduto et al[17]	68	Exercise testing	Not reported
Berger et al 1979[19]	73	Exercise testing	Not reported
Distante et al[20]	12	Patients with Prinzmetal's angina (spontaneous angina, or induced by ergonovine)	Not reported

of the ischaemic cascade tend to adopt an approach to ischaemia testing that is driven by an underlying pretest suspicion as to the likelihood of ischaemia. For example a negative ischaemia test in a patient with typical angina will trigger a further investigation, with a test that may not necessarily be upstream the cascade. This behaviour is not consistent with trust in an ischaemic cascade. It suggests that physicians are ready to accept that it is biologically plausible that both tests are 'correct' but having different results. Clinically this means that physicians may tailor the use of specific ischaemia tests to specific populations.[36] However, this contrasts with clinical trials comparing ischaemia tests in which investigators appoint a 'gold standard', which is assumed to be the most sensitive test in all patients.[37 38] Such an approach does not appreciate variation between individuals and therefore squanders an opportunity to understand which tests are most appropriate for specific populations.

SCIENTIFIC AND CLINICAL IMPLICATIONS

The scientific and clinical implications of a 'constellation' model of ischaemia, rather than the 'cascade' model, are pertinent to the key question of whether ischaemia is present when two tests have conflicting results. This is a common challenge in the interpretation of validation studies of new tests of ischaemia. Currently any disagreement of the new test with the test appointed

as 'gold standard' is interpreted as an inaccuracy of the new test. Recently this approach has been demonstrated to be flawed.[35 39]

A 'constellation' model of ischaemia could provide a solution to the problem of how to interpret investigations when conflicting test results coexist in the same patient and thereby resolve a crisis for those relying on the ischaemic cascade as a schema for interpretation of events. The constellation would suggest that in such a situation both tests may be correct, but one biological event may have occurred at a lower degree of ischaemia than the other event in that particular individual. Importantly, the converse may be true in another individual—a possibility that cannot be encompassed with a cascade.

The 'constellation' does not provide a solution to the problem of how to differentiate a false-positive test from the situation of conflicting results from two tests in the same patient. One way to resolve this would be a study design that doesn't simply compare one test to another, but evaluates the test's ability to predict improvement of symptoms when the patient receives appropriate therapy, such as antianginal medications. For example, a trial design that may help evaluate the clinical accuracy of a test may involve randomising patients, who test negative or positive for an investigation of ischaemia, to antianginal medications or placebo, and measuring symptomatic and or functional outcomes (figure 4). An objective

Table 2 Summary of human studies illustrating the concept of the ischaemic constellation

| Study	Sample size	Ischaemic state	Blinded study
Choy et al[32]	707	Dobutamine or bicycle ergometer stress echocardiography	Not reported
Sigwart et al[12]	12	Coronary artery occlusion	Not reported
Levy et al[18]	25	Exercise testing	Not reported
Amsterdam et al[16]	92	Exercise testing	Not reported
Gaspardone et al[33]	21	Dipyridamole infusion	Yes
Cannon et al[34]	42	Dobutamine infusion	No
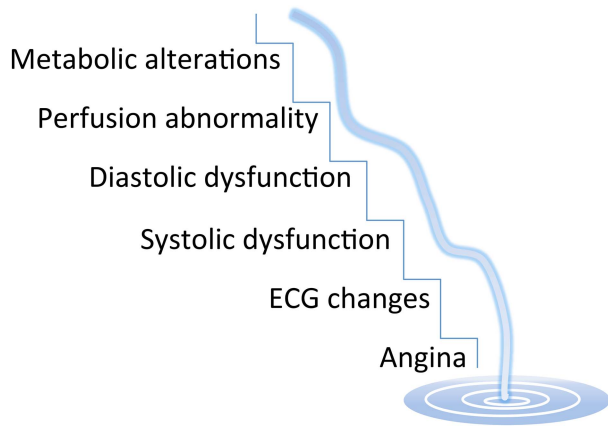
Figure 3 Waterfall analogy of the ischaemic cascade. In a cascade the water falling down one step is the water that is available to later fall down the next step. The water must fall down the steps in sequence. If water was found to be moving out of sequence, that is, up and down between steps in an unpredictable way, then it is not a cascade.

assessment of patient functional status such as cardiopulmonary exercise testing could be used to assess the patient's symptoms and functional capacity, thus providing an objective, reproducible and quantifiable measure. The most reliable test would be that which most consistently predicts whether the patient will improve symptomatically, or functionally (in patients with 'silent' ischaemia), with treatment versus placebo. Such an approach uses the patient's symptoms and functional capacity (with placebo control) as the reference standard.

It should be noted that there are several different causes of ischaemia and therefore, the treatment success of individual pharmacological agents will vary according to the cause of ischaemia. Our study design would therefore require identification of the predominant cause of ischaemia prior to enrollment of the patients into the
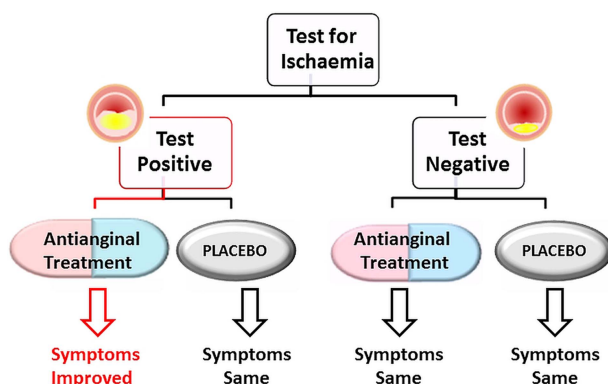
study. For example, separating those with angina and epicardial coronary disease from those with angina and 'normal' epicardial arteries. This is not unusual in this field, for example the fractional flow reserve (FFR) studies have routinely stipulated a minimum amount of epicardial disease that patients must have prior to enrollment.[40–42]

The external applicability of a clinical trial result to different patient populations applies to all clinical studies. The efficacy of any given treatment will vary according to the individual characteristics of the population being treated. While our study design addresses the concept of an ischaemic constellation the external applicability of its results to different patient populations will be vulnerable to the limitations of any clinical trial. While this has been commonly acknowledged in pharmacology studies (eg, ACE inhibitors in black vs white populations[43]) it is only now being more widely acknowledged in the ischaemia diagnostic domain. Recent studies have confirmed that the accuracy of diagnostic tests will vary according to the underlying distribution of stenoses in differing populations.[44] Furthermore, the treatment threshold of certain diagnostic tests may vary according to age and gender.[45 46]

Despite the above limitations, which are shared with existing trial design, the constellation model begins the process of acceptance that a single gold standard test for ischaemia may not be possible. The reasoning above suggests that there may well be multiple tests, each individually accurate in describing one facet of the constellation, but mutually conflicting without any necessarily being erroneous. Explicit public recognition of this might open the way for clinicians to interpret studies comparing ischaemia tests in a more rational manner. A first step to permitting this personalised and integrative cardiology would be to recognise that information from these quantitative tests is continuous rather than dichotomous.

SUMMARY

In this review we have indicated that (1) it is unwise to describe the clinical manifestations of ischaemia as a cascade, (2) it may be unwise to speak of the sensitivity or specificity of a test for ischaemia, since there may be no true gold standard and (3) when the results of clinical tests differ we may need to take a more sophisticated approach than saying one is right and the other is wrong.

Figure 4 Illustration of a trial design to help evaluate the clinical accuracy of a test of ischaemia. The best test would result in improved symptoms in those patients who test positive and are randomised to antianginal treatment, with no change in symptoms in those who test positive and are randomised to placebo, or after treatment for those who test negative.

CONCLUSION

For decades the ischaemic cascade has been at the foundations of teaching regarding diagnosis of ischaemia. Review of the source literature suggests, however, that it is not correct, with components of the cascade often occurring out of sequence. Presenting information known to be incorrect may be convenient for the short-term aim of providing educational content, but does not

necessarily help the long-term aim of improving scientific knowledge about important processes in humans.

We propose the 'ischaemic constellation', a paradigm that recognises no single gold standard test for ischaemia and that different markers of ischaemia may become abnormal at different stages depending on the individual, the nature of stimulus to ischaemia, and other factors, and that results may vary between one episode and another. This 'constellation concept' calls for a new way of evaluating ischaemia tests that places the patient as the 'gold standard'.

REFERENCES

1. Nesto RW, Kowalchuk GJ. The ischaemic cascade: temporal sequence of haemodynamic electrocardiographic and symptomatic expressions of ischaemia. *Am J Cardiol* 1987;57:23C–30C.
2. Theroux P, Ross J Jr, Franklin D, et al. Coronary arterial reperfusion. III. Early and late effects on regional myocardial function and dimensions in conscious dogs. *Am J Cardiol* 1976;38:599–606.
3. Sabbah HN, Stein PD. Early segmental thinning of the left ventricular wall following regional ischaemia. *Cathet Cardiovasc Diagn* 1983;9:473–82.
4. Kerber RE, Marcus ML, Ehrhardt J, et al. Correlation between echocardiographically demonstrated segmental dyskinesis and regional myocardial perfusion. *Circulation* 1975;52:1097–104.
5. Pandian NG, Kieso RA, Kerber RE. Two-dimensional echocardiography in experimental coronary stenosis. II. Relationship between systolic wall thinning and regional myocardial perfusion in severe coronary stenosis. *Circulation* 1982;66:603–11.
6. Leong-Poi H, Rim SJ, Le E, et al. Perfusion versus function: the ischaemic cascade in demand ischemia implications of single vessel versus multivessel stenosis. *Circulation* 2002;105:987–92.
7. Mor-Avi V, Collins KA, Korcarz CE, et al. Detection of regional temporal abnormalities in left ventricular function during acute myocardial ischemia. *Am J Physiol Heart Circ Physiol* 2001;280:H1770–81.
8. Heyndrickx GR, Baig H, Nellens P, et al. Depression of regional blood flow and wall thickening after brief coronary occlusions. *Am J Physiol* 1978;234:H653–9.
9. Lafitte S, Matsugata H, Peters B, et al. Comparative value of dobutamine and adenosine stress in the detection of coronary stenosis with myocardial contrast echocardiography. *Circulation* 2001;103:2724–30.
10. Alam M, Khaja F, Brymer J, et al. Echocardiographic evaluation of left ventricular function during coronary artery angioplasty. *Am J Cardiol* 1986;57:20–5.
11. Hauser AM, Gangadharan V, Ramos RG, et al. Sequence of mechanical electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: echocardiographic observations during coronary angioplasty. *J Am Coll Cardiol* 1985;5:193–7.
12. Sigwart U, Grbic M, Payot M, et al. Ischaemic events during coronary artery balloon obstruction. In: Rutishauser W, Roskamm H, eds. *Silent myocardial ischaemia*. Berlin: Springer-Verlag, 1984:29–36.
13. McLaurin LP, Rolett EL, Grossman W. Impaired left ventricular relaxation during pacing-induced ischaemia. *Am J Cardiol* 1973;32:751–7.
14. Iskandrian AS, Bemis CE, Hakki AH, et al. Ventricular systolic and diastolic impairment during pacing induced myocardial ischaemia in coronary artery disease: simultaneous haemodynamic, electrocardiographic and radionuclide angiographic evaluation. *Am Heart J* 1986;112:382–91.
15. Aroesty JM, McKay RG, Heller GV, et al. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischaemia. *Circulation* 1985;71:889–900.
16. Amsterdam EA, Martschinske R, Laslett LJ, et al. Symptomatic and silent myocardial ischaemia during exercise testing in coronary artery disease. *Am J Cardiol* 1986;58:43B–6B.
17. Reduto LA, Wickemeyer WJ, Young JB, et al. Left ventricular diastolic performance at rest and during exercise in patients with coronary artery disease: assessment with first-pass radionuclide angiography. *Circulation* 1981;63:1228–37.
18. Levy RD, Shapiro LM, Wright C, et al. Haemodynamic response to myocardial ischaemia during unrestricted activity, exercise testing, and atrial pacing assessed by ambulatory pulmonary artery pressure monitoring. *Br Heart J* 1986;58:12–18.
19. Berger HJ, Reduto LA, Johnstone DE, et al. Global and regional left ventricular response to bicycle exercise in coronary artery disease: assessment by quantitative radionuclide angiocardiography. *Am J Med* 1979;66:13–21.
20. Distante A, Rovai D, Picano E, et al. Transient changes in left ventricular mechanics during attacks of Prinzmetal's angina: an M-mode echocardiographic study. *Am Heart J* 1984;107:465–74.
21. Weustink AC, de Feyter PJ. The role of multi-slice computed tomography in stable angina management: a current perspective. *Neth Heart J* 2011;19:336–43.
22. Conti CR, Bavry AA, Petersen JW. Silent ischemia: clinical relevance. *J Am Coll Cardiol* 2012;59:435–41.
23. Beller GA. Myocardial perfusion imaging for detection of silent myocardial ischemia. *Am J Cardiol* 1988;61:22F–6F.
24. Detry JM. The pathophysiology of myocardial ischaemia. *Eur Heart J* 1996;17(Suppl G):48–52.
25. Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
26. Hyodo E, Muro T, Hozumi T, et al. Observation of the ischaemic cascade in humans using contrast echocardiography during dobutamine stress. *Circ J* 2003;67:406–10.
27. Nixdorff U, Erbel R, Wagner S, et al. Dynamic stress echocardiography for evaluating anti-ischemic drug profiles in post-MI patients. *Int J Card Imaging* 1997;13:485–91.
28. Williams KA, Sherwood DF, Fisher KM. The frequency of asymptomatic and electrically silent exercise-induced regional myocardial ischaemia during first pass radionuclide angiography with upright bicycle ergometry. *J Nucl Med* 1992;33:359–64.
29. Heller GV, Ahmed I, Tilkemeier PL, et al. Comparison of chest pain, electrocardiographic changes and thallium-201 scintigraphy during varying exercise intensities in men with stable angina pectoris. *Am J Cardiol* 1991;68:569–74.
30. Sestito A. Lamendola P, DiFranco A, et al. Is dipyridamole stress echocardiography able to induce ischemic cascade in patients with chronic stable angina? European Heart Journal Cardiovascular Imaging. Conference: 16th Annual Meeting of the European Association of Echocardiography, EUROECHO 2012 Athens Greece. 13 (pp i173), 2012. [Conference Abstract].
31. Kyrzopoulos S, Tsiapras D, Domproglou G, et al. Diastolic dysfunction precedes systolic deterioration in dobutamine stress echocardiography studies. European Journal of Echocardiography. Conference: 14th Annual Meeting of the European Association of Echocardiography Copenhagen Denmark. 11 (pp ii101), 2010. [Conference Abstract].
32. Choy JB, Linton S, Pompa N, et al. Physiologic changes during myocardial stress echocardiography: is the ischemic cascade important? Journal of the American College of Cardiology. Conference: 60th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC, 11 New Orleans, LA United States. 57 (14 Suppl 1) (pp E762), 2011 [Conference Abstract].
33. Gaspardone A, Chiariello L, Crea F, et al. Temporal sequence and spatial distribution of ischaemic changes during Dipyridamole Stress Test—the key role of microvascular dysfunction. *J Clin Basic Cardiol* 2005;8:47–53.
34. Cannon RO III, Curiel RV, Prasad A, et al. Comparison of coronary endothelial dynamics with electrocardiographic and left ventricular contractile responses to stress in the absence of coronary artery disease. *Am J Cardiol* 1998;82:710–14.

35. Sen S, Asrress KN, Nijjer S, *et al*. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration. Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study). *J Am Coll Cardiol* 2013;61:1409–20.

36. Judelson DR. Examining the gender bias in evaluating coronary disease in women. *Medscape Womens Health* 1997;2:5.

37. Berry C, van 't Veer M, Witt N, *et al*. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. *J Am Coll Cardiol* 2013;61:1421–7.

38. Jeremias A, Maehara A, Généreux P, *et al*. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *J Am Coll Cardiol* 2014;63:1253–61.

39. Petraco R, van de Hoef TP, Nijjer S, *et al*. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). *Circ Cardiovasc Interv* 2014;7:492–502.

40. Tonino PA, De Bruyne B, Pijls NH, *et al*. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213–24.

41. De Bruyne B, Pijls NH, Kalesan B, *et al*. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991–1001.

42. Bech GJ, De Bruyne B, Pijls NH, *et al*. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation* 2001;103: 2928–34.

43. Forman JP, Price DA, Stevanovic R, *et al*. Racial differences in renal vascular response to angiotensin blockade with captopril or candesartan. *J Hypertens* 2007;25:877–82.

44. Petraco R, Escaned J, Sen S, *et al*. Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry. *EuroIntervention* 2013;9: 91–101.

45. Kim HS, Tonino PA, De Bruyne B, *et al*. The impact of sex differences on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy. *JACC Cardiovasc Interv* 2012;5:1037–42.

46. Lim HS, Tonino PA, De Bruyne B, *et al*. The impact of age on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial substudy. *Int J Cardiol* 2014;177:66–70.