This issue of Heart and Metabolism is dedicated to a core aspect of cardiology, revascularization. Although atherosclerosis is often viewed as a seemingly simple plumbing problem, this issue highlights the complexity of the underlying coronary physiology and the multiple pathways that can lead to myocardial ischemia. For patients with stable angina, these complexities act in concert to influence decisions regarding revascularization. To appreciate these complexities better, and to enjoy the content of this issue, it is best to read the articles in an order that differs from our stereotypical layout.

The historic journey from early physiology to present day percutaneous and surgical revascularization is beautifully told in the Refresher Corner article by Spencer King. We are privileged to have the story explained by someone so intimately involved with the evolution of revascularization. This unusual Refresher Corner uses the history of revascularization as a backdrop to the dilemmas that now face cardiologists in interpreting the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) and the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trials. These trials, and their impact on contemporary practice, are a theme that echoes through all the articles in this issue.

My recommendation would be to continue your journey by reading the Basic Article by Maria Siebes on coronary physiology beyond the stenosis. This article concisely and precisely introduces the complexities of the vascular and myocardial contributions to coronary artery blood flow and its distribution to the distal myocardium. The concepts are summarized and interlinked in a way that reveals the author as one the doyennes of coronary physiology. Particularly compelling is the enormous effect that very small changes in minimal lumen diameter of a stenosis have on its resistance, and how in turn this affects the distal microvasculature due to the pressure dependence of autoregulation and hyperemic “minimal” microvascular resistance. At the end of reading this article you will be convinced that lumenography is a crude basis for decision-making. This view is greatly aided by the author introducing and explaining the current clinical and experimental physiological indices of stenosis severity and microvascular function. The concepts are very well illustrated and reinforced by the figures within this article and they provide a firm foundation to the Case Report, which I recommend as the next stop on the journey through this issue.

The Case Report by Paola Capozza and Giancarlo Todiere involves two patients with similar acute presentations with myocardial ischemia but with very different causative pathologies.
These cases serve to highlight that it is not the coronary artery but the myocardium that should be the focus/center of our attention and analyses. This shift in focus is given a Copernican paradigm with myocardial ischemia at the center of a newly appreciated solar system. Within this solar system there are numerous orbiting planets of which atherosclerotic fixed stenosis is only one of the numerous pathologies that can lead to myocardial ischemia; in isolation or, much more commonly, in concert with other pathologies affecting microvascular resistance and/or blood rheology. This shift in focus, away from atherosclerotic stenosis and towards an integrative view of the effects of varied pathologies on the myocardium, is reinforced in the Metabolic Imaging article.

Declan O’Regan and Stuart Cook are interested in the biochemical consequences of myocardial ischemia and how these can be interrogated by magnetic resonance imaging (MRI). A deficit in myocardial perfusion, whether imaged by a radionuclide, echo contrast or MRI, is often equated with ischemia. However, it is important to remember that all that is being highlighted are heterogeneities in myocardial perfusion, usually by the presence of vasodilating stressors. In contrast, the processes discussed in this article rely on physical/chemical changes in the composition of the myocardium that occur as a direct consequence of ischemia. These changes are revealed using specific MRI pulse and acquisition sequences, (T2 edema imaging) or contrast agents, (late gadolinium enhancement). The former provides a signature of the volume of myocardium that was ischemic and the latter the volume that is irreversibly injured (infarcted). Individually, these imaging modalities can be used to provide more detailed information about the etiology of chronic and acute heart disease. In combination, the authors illustrate how these imaging techniques provide a measure of myocardial salvage and can be used as surrogate endpoints in clinical trials. Detailed phenotyping of this kind would have been useful in the cases reported by Paola Capozza and Giancarlo Todiere; however, they can also probably be used to individualize management using lessons learnt from clinical trials. Finally, this brings us to the heart of this issue – how to select patients for revascularization.

In the New Therapeutic Approaches article by Christian Seiler we are reminded through his group’s seminal work that endogenous collaterals are common, but the support they provide shows considerable individual variability. Other than exercise, and perhaps enhanced external counterpulsation, there are no reliable means to enhance this support and so far trials delivering angiogenic factors have failed to bring any clinical improvement. Therefore, at present, the only viable means of revascularization is by percutaneous coronary intervention (PCI) and coronary artery bypass surgery. The PCI and coronary artery bypass surgery trials mentioned by Spencer King are expanded on in the Main Clinical article by Mandeep Sidhu and William Boden and in Hot Topics by Alda Huqi. The Main Clinical article focusses on the COURAGE, BARI-2D and the Surgical Treatment for Ischemic Heart Failure (STITCH) trials and how their findings can be used to interpret the New York State PCI Registry and FAME 2. Similarly, Alda Huqi takes a very analytical and sideways look at the messages these trials communicate and the biases that may undermine registries and even FAME 2. The authors of both these articles come to similar, coherent and compelling conclusions. In patients with stable angina optimal medical therapy can be safely used first line and revascularization can be reserved for those that have quality of life-limiting symptoms despite maximal therapy. Old and new evidence suggests surgical revascularization is favored in patients with diabetes while β-blocker use can be reviewed in those patients with preserved left ventricular function who have not had an acute cardiac event in the past year. Is it really that simple?
Coronary flow and physiology beyond the stenosis

Maria Siebes, Department of Biomedical Engineering and Physics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Correspondence: Dr Maria Siebes, Department of Biomedical Engineering and Physics, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
Tel: +31 (20) 566-7240, fax: +31 (20) 0691-7233
e-mail: m.siebes@amc.uva.nl

Abstract
Blood flow in the coronary circulation is normally well regulated and able to meet even strenuous demand. The presence of an epicardial stenosis poses multiple challenges for safeguarding coronary blood flow and myocardial perfusion, which is further exacerbated by the concurrent presence of microvascular disease. The ability to adjust flow adequately during physiological stress is compromised and myocardial perfusion is redistributed away from the subendocardium. Recent technological advancements have enabled the invasive quantification of epicardial and microvascular pathologies in the catheterization laboratory by intracoronary hemodynamic measurements. The advantages and disadvantages of the various approaches are presented on the basis of the underlying physiological models. Among these, combined measurements of pressure and flow velocity yield more comprehensive information on the functional effect of a stenosis and the status of the downstream microvascular compartment. This article will give a brief overview of coronary physiology, with a focus on the role of microvascular resistance in diagnosis and treatment evaluation.

Keywords: Control of coronary blood flow; coronary artery stenosis; coronary microcirculation; myocardial perfusion; pressure-flow relation

Introduction
The heart muscle is continuously active and needs a constant supply of oxygen and metabolic substrates. Because oxygen extraction is already near maximal at rest, increased oxygen demand must be matched by augmenting coronary blood flow, which is intrinsically regulated to meet dynamic changes in metabolic requirements [1]. Myocardial perfusion via the coronary circulation is governed by an integrated system of control mechanisms [2]. Adverse alterations in form (stenosis) or function (microvascular disease) of the coronary vessels lead to clinical disorders ranging from ischemic episodes to myocardial infarction, with serious consequences for the long-term cardiovascular prognosis of the patient. Arteriolar dilation to compensate for the pressure loss across a developing stenosis is an important mechanism to prevent myocardial ischemia, but coronary vasodilator reserve is progressively compromised with increasing stenosis severity. The effect of an epicardial obstruction thus extends beyond the stenosis into the microcirculation and alters transmural perfusion as well as cardiac–coronary interaction. Although the clinical assessment of stenosis severity has advanced beyond the visual
determination of the anatomical narrowing, the current methods are affected by the concurrent presence of microvascular dysfunction.

Coronary flow beyond the stenosis
The coronary circulation can conceptually be regarded as a series of resistive compartments, the large epicardial conduit vessels, the arterial resistance vessels, and the vasculature comprising capillaries and small veins. Epicardial vessels only account for about 5% of total coronary resistance. Coronary pressure mainly dissipates along the smaller arteries (300–100 μm) and arterioles (<100 μm) [3]. Figure 1 shows a 2 mm thick transverse slice of a dog heart, illustrating the arrangement of the coronary vasculature in the myocardium [4].

As schematically illustrated in Figure 2, coronary blood flow at rest is matched to myocardial oxygen demand (metabolic adaptation) and closely maintained to counteract variations in perfusion pressure (autoregulation) by adjusting microvascular tone via an orchestrated sequence of control mechanisms [5]. When vascular tone is minimized by potent vasodilators, coronary flow becomes dependent on perfusion pressure and coronary resistance at maximal vasodilation, further denoted as hyperemic microvascular resistance (HMR), is essentially determined by microvascular structure (diameter and length) rather than function (tone). According to the law of Poiseuille, the resistance of a blood vessel is determined by its length, blood viscosity and, most importantly, its diameter, which inversely relates to resistance with its fourth power. As vessels without tone are essentially elastic conduits, their diameter is pressure dependent [6] and resistance to flow increases with decreasing perfusion pressure [7]. HMR is therefore not constant. Often the inverse slope of the pressure–flow relation is considered erroneously to reflect coronary vascular resistance; however, resistance is pressure drop divided by flow and this ratio varies over the range of the hyperemic pressure–flow relation because of its non-zero pressure intercept.

An epicardial stenosis forms an additional resistance and impedes an adequate increase in flow or can even reduce resting perfusion once the autoregulatory capacity is exhausted. In straight blood vessels,

---

**Fig. 1** Architecture of coronary microvessels in a dog heart. These 3-dimensional data were obtained by alternately cutting and imaging (at 40 μm resolution) the frozen specimen, which was infused with fluorescent vascular casting material. Note the intricate arrangement of coronary microvessels as they penetrate into the cardiac muscle.

**Fig. 2** Coronary pressure–flow relationship. At rest, flow is maintained over a large range of physiological pressures by a parallel change in resistance. The dashed line indicates autoregulation at higher oxygen consumption. At maximal vasodilation, flow can increase up to about five times in the absence of a stenosis (grey vertical line). Control is exhausted and coronary flow depends on perfusion pressure. As vascular tone is minimal, vessel diameter decreases with reduced distending pressure. The nonlinear pressure loss across a stenosis (red dotted lines) drastically reduces the maximal flow that can be achieved. Note that the maximal pressure–flow line has a non-zero intercept, which implies that microvascular resistance is pressure dependent. MVO₂ = myocardial oxygen consumption.
pressure is lost by viscous friction along the narrowed lumen. In addition, the diameter reduction induces convective acceleration in the throat, yet only a fraction of the pressure converted into kinetic energy (law of Bernoulli) is recovered at the exit. Since kinetic energy relates to the square of velocity, the total pressure loss across a stenosis follows a quadratic function of flow \[8\], as indicated by the curvilinear dotted relations in Figure 2. Both the viscous and exit pressure loss relate to the inverse fourth power of the minimal stenosis diameter, rendering a subclinical stenosis critical with only little further reduction in lumen diameter. Recall that the diameter of passive vessels decreases with lower distending pressure, such as distal to a stenosis, thereby increasing HMR. Conversely, revascularization of an epicardial lesion is associated with a gain in distal perfusion pressure and a beneficial reduction in coronary microvascular resistance during hyperemia \[9\].

Note that Figure 2 only depicts a certain condition. The group of stenosis curves may shift to the right in case of a higher systemic pressure. However, this does not necessarily imply an increase in vasodilator reserve, because higher arterial pressure requires more cardiac work and a higher level of flow at rest. Similarly, both the position and slope of the hyperemic pressure–flow line depend on cardiac function \[10\]. A rightward shift (e.g. by elevated heart rate) and a decreased slope (e.g. by myocardial hypertrophy) both serve to increase microvascular resistance and decrease flow reserve.

### Myocardial perfusion beyond the stenosis

Perfusion relates to the amount of blood passing through the capillaries in a piece of tissue of certain weight and is expressed in mL/s/g. Myocardial perfusion is profoundly heterogeneous at multiple spatial scales \[11–13\]. Major causes include heterogeneity in local oxygen consumption and the asymmetric branching of the intramural vascular tree. A consequence of micro-heterogeneity is that pieces of tissue where vasodilatory reserve is exhausted due to a proximal stenosis co-exist with areas that still have reserve \[14\]. This explains why adenosine may still be able to increase macrovascular flow despite local ischemia, and may account for the micronecrosis seen with chronic ischemia \[15\]. Regional differences are predominantly caused by compressive forces on intramural vessels exerted by cardiac contraction, often referred to as the extravascular resistance component. The dynamics of the contraction process introduce a transmural gradient in tissue pressure, which is high at the subendocardium and declines towards the epicardium. The intramural blood volume expelled during systole is restored in diastole as the muscle relaxes and tissue pressures return to diastolic levels. Intramural blood volume amounts to 15–20% of tissue volume and depends on the same factors that determine the extravascular resistance component. The variations of intramural volume throughout the heartbeat amount to 10–20% of average intramural blood volume and are responsible for the out-of-phase flow waveforms in coronary arteries and veins.

The subendocardium is especially vulnerable to ischemia. At hyperemia the ratio of subendocardial-to-subepicardial perfusion (at a coronary pressure of 100 mm Hg) equals 1.0 at a heart rate of 80 bpm. In the arrested heart, this ratio is about 1.5, but it decreases to about 0.5 at a heart rate of 180 bpm \[16\]. Therefore, subendocardial hyperemic resistance can vary by a factor of three as a function of heart rate. Progressive reduction of coronary perfusion pressure by an epicardial stenosis causes a reduction of the subendocardial/subepicardial blood flow ratio and a redistribution of blood flow away from the subendocardium \[17\]. The loss of flow reserve at low perfusion pressures is thus most pronounced at the subendocardium, and is further exacerbated at higher heart rates due to the reduction in relative diastolic duration \[18\]. These spatial differences in myocardial perfusion go unnoticed by epicardial hemodynamic measurements.

### Clinical assessment

From the above considerations it is obvious that angiographic stenosis dimensions alone are too limited in defining the functional significance of an epicardial lesion, which ultimately depends on the complete hemodynamic picture at the time of assessment. Current technology allows for the invasive quantification of flow velocity and/or pressure in the catheterization laboratory by a sensor-equipped guide wire \[19, 20\]. An alternative method employs thermodilution to assess coronary volume flow \[21\], but this approach involves additional infusion equipment and procedural steps, and yields only mean values, while the pulsatile patterns obtained with a Doppler velocity probe contain useful clinical information. Furthermore, velocity is
a more robust measure and relatively independent of sensor position along the vessel, while volume flow diminishes after every side branch.

Flow through the coronary circulation is distinct from blood flow in systemic arteries due to the “squeezing” effect of cardiac contraction on the microvessels embedded in the myocardium [22]. As a result, pressure and flow are out of phase, with maximal flow during diastole as perfusion pressure declines. Typical coronary signals obtained in a patient (Fig. 3) demonstrate the changes in pulsatile pressure and velocity waveforms induced by distal vasodilation with adenosine. The marked increase in diastolic flow in the healthy vessel barely induces a larger pressure gradient along the vessel (top panels). In contrast, systolic–diastolic flow differences become damped by a stenosis, and a modest increase in flow velocity after adenosine administration is accompanied by a large decrease in distal pressure (bottom panels).

These signals form the basis for the clinical evaluation of functional stenosis severity and microvascular disease [23]. Depending on whether pressure, velocity, or combined signals are obtained, different indices are used to arrive at a clinical decision. The most widely used parameter is fractional flow reserve (FFR), which is defined as the maximum myocardial flow in the stenotic territory divided by the maximum myocardial flow in the same territory in the theoretical case of a normal epicardial vessel. In practice, this flow ratio is assessed from the ratio of distal to proximal pressure at maximal hyperemia based on the fundamental assumption that minimal microvascular resistance in those two conditions is constant and cancels out of the equation [20]. The underlying model of FFR does not concur with the physiological principles discussed above, and relies heavily on collateral flow to explain the fact that the hyperemic coronary pressure–flow line does not pass through the origin, rather than considering the effect of cardiac contraction on perfusion [24]. Notwithstanding the physiological shortcomings, the clinical success of FFR in a variety of patient subsets confirms that even pressure-only functional information trumps anatomical assessment for the decision about stenosis revascularization [25].

Hyperemic stenosis resistance (HSR) has been introduced by our group and equals stenosis pressure drop divided by flow velocity distal of the stenosis. Utilizing combined information of pressure and velocity consistently yielded a higher prediction of inducible ischemia than FFR [26], and HSR was shown to be rather

**Fig. 3** Coronary pressure and velocity waveforms measured in a patient at rest and hyperemia (right) in the absence (top) and presence (bottom) of a stenosis. At baseline, coronary flow was hardly affected by the stenosis, albeit at a higher pressure loss. During hyperemia, flow increased almost 3-fold without a stenosis, with barely additional pressure loss. In contrast, the pressure gradient more than doubled in the presence of a stenosis, with only a modest increase in flow.
independent of HMR in contrast to FFR [27]. A practical disadvantage of HSR is that combined assessment of distal pressure and flow velocity is required, which is, however, possible with a dual-sensor guide wire. On the other hand, HSR assessment has the added benefit that HMR is also obtained [9,19]. Combined measurement of pressure and flow velocity may therefore provide new insight into the balance between epicardial and microvascular disease in a specific patient (Fig. 4). Pulsatile coronary pressure and flow velocity waveforms are significantly altered by an epicardial stenosis, at a degree of obstruction much less than that required for a reduction in mean flow. Variations in coronary pressure and velocity pulses also reflect the mechanical influence of cardiac–coronary interaction and have been investigated using wave intensity analysis for a variety of conditions [28–30].

While the FFR field focuses on means to achieve the mandatory maximal hyperemia, alternative developments have started to evaluate the physiological significance of a stenosis without the need for potent vasodilators. One of them is the baseline stenosis resistance (BSR), the stenosis resistance measured at resting flow, which performed similarly well to FFR against a noninvasive test of reversible ischemia [31]. Also the instantaneous diastolic pressure ratio (iFR) has been presented as a new index [32] and several multicenter studies have been designed to study its efficacy.

Conclusions

This paper has provided a short overview of the principles of coronary physiology and its implications for the functional diagnosis of coronary artery stenosis derived from epicardial hemodynamic measurements. Noninvasive imaging modalities such as perfusion magnetic resonance imaging have not been discussed, but these are very promising and obviously directly related to the mechanisms underlying myocardial perfusion. Coronary flow reserve remains an important physiological concept but its direct clinical application is hampered by its dependence on flow at rest, which is variable. The focus is shifting from stenosis evaluation alone to the assessment of both epicardial and microvascular disease.

Acknowledgements

This work was supported by the Netherlands Heart Foundation (2006B186) and by the European Community’s 7th Framework Program (ICT-2007-224495: euHeart).

References


Fig. 4 Screenshot of the instrument console (Combomap®, Volcano, USA) showing the relevant pressure and velocity signals and hemodynamic indices obtained in a reference vessel of a patient. CFR = coronary flow reserve, FFR = fractional flow reserve, HMR = hyperemic microvascular resistance, HSR = hyperemic stenosis resistance.
Does revascularization work?

Mandeep S. Sidhu and William E. Boden, Albany Stratton VA Medical Center, Albany Medical Center, Albany Medical College, Albany, New York, USA

Correspondence: Dr William E. Boden, Samuel S. Stratton VA Medical Center, 113 Holland Street, Albany, NY 12208, USA
Tel: 518-626-6386, fax: 518-626-6511
e-mail: william.boden@va.gov

Abstract
It is well established and accepted, based on the results of multiple randomized controlled trials (RCTs), that myocardial revascularization in patients with acute ST-segment elevation myocardial infarction (MI) and other acute coronary syndromes (ACS) results in improved outcomes, both in terms of reduced short and long-term mortality as well as rates of subsequent MI. By contrast, it is less clear that myocardial revascularization in patients with stable ischemic heart disease (SIHD) is associated with an improvement in clinical outcomes when compared to optimal medical therapy. Several RCTs in SIHD patients over the past several years, including well-conducted meta-analyses of these clinical trials, have universally failed to show an improvement in death, MI, or other “hard” clinical outcomes. While clinical event reduction is certainly not the only goal of myocardial revascularization, its notable absence in SIHD, as compared with ACS patients certainly provides pause for thought when deciding on the initial treatment strategy for a given patient with chronic stable angina or SIHD.

Keywords: Coronary artery disease; myocardial revascularization; optimal medical therapy; stable ischemic heart disease

The provocative question posed by the title of this paper forces us to confront critically the question of the patient and the circumstance in which revascularization improves outcomes. When clinicians are faced with this important question, two critical issues need to be considered and addressed: (1) will revascularization reduce rate of mortality and/or myocardial infarction (MI)?; (2) will revascularization improve angina and quality of life compared with medical therapy? In addressing these questions, physicians must also ask whether these goals can be achieved in all cardiac patients, or whether these therapeutic goals apply differentially to subpopulations of coronary artery disease (CAD) patients? In particular, when should revascularization be the initial management strategy and when should it be reserved for patients who cannot be managed with optimal medical therapy (OMT).

There is an abundance of evidence that revascularization is not only indicated but necessary to achieve optimal clinical outcomes in patients with acute coronary syndromes (ACS) such as ST-segment elevation myocardial infarction (STEMI) or high-risk non-STEMI, as outlined in the 2009 and 2013 American College of Cardiology/American Heart Association guidelines for the management of STEMI [1]. Furthermore, emergent/urgent percutaneous coronary intervention (PCI) has been shown to result in established clinical benefits in certain ACS patients [2, 3].
There is compelling scientific evidence that total or subtotal coronary occlusion immediately following plaque rupture or fissuring cannot be optimally managed with medical therapy alone. Therefore, in these clinical scenarios, it is clear that acute myocardial revascularization reduces mortality, the risk of recurrent MI, and preserves left ventricular function. In other words, revascularization in ACS patients is “disease modifying” and clearly “works” from the important perspective of cardiac event reduction, based on both short and long-term clinical benefit and prognostic improvement in these patient populations.

By contrast, the utilization of revascularization in the chronic angina or stable ischemic heart disease (SIHD) population raises a more complex and relevant question as to the optimal clinical decision-making. There is discordant evidence from clinical trials and observational studies in patients with SIHD, notably several randomized controlled trials (RCTs), such as the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [4], the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) [5] and the Japan Stable Angina Pectoris (JSAP) study [6], as well as numerous meta-analyses of these RCTs, including a very recent meta-analysis of stent trials in the era of modern medical therapy published in the *Archives of Internal Medicine* [7]. All these studies have failed to demonstrate any incremental clinical benefit for PCI above and beyond OMT alone for the reduction of death or nonfatal MI, hospitalization for ACS, the need for unplanned revascularization and a durable, sustained effect on angina relief – findings quite in contrast to those achieved with PCI in acute MI or ACS patients.

For patients with chronic stable angina and SIHD, the COURAGE trial [4] and the BARI-2D trial [5] both support the management of patients with an initial trial of optimal pharmacotherapy, lifestyle interventions focused on improving dietary consumption and increasing exercise, as well as secondary prevention instead of immediate revascularization as is commonly performed in these populations of chronic stable angina and SIHD. It is best to review the data from these individual trials in order to examine further this important question regarding the effectiveness of revascularization.

In COURAGE, 2287 patients with objective evidence of myocardial ischemia and significant coronary disease at coronary angiography were randomly assigned to PCI with OMT versus OMT alone. The rate of the primary endpoint (all-cause mortality or non-fatal MI) during follow-up which ranged from 2.5 to 7.0 years with a median of 4.6 years, and was similar between the PCI and OMT groups (with cumulative primary event rates of 19.0% and 18.5%, respectively, with a hazard ratio (HR) of 1.05 for the PCI group and a 95% CI of 0.87 to 1.27; *P* = 0.62). Therefore, as an initial management strategy in patients with stable CAD, PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to OMT alone.

Subsequently, in 2009, the BARI-2D trial [5] enrolled 2368 patients with both type 2 diabetes and SIHD who were randomly assigned in a 2 × 2 factorial design to undergo either prompt revascularization with intensive medical therapy or intensive medical therapy alone, and to undergo either insulin sensitization or insulin provision therapy. The results demonstrated that, at a mean follow-up of 5 years, rates of survival (88.3% versus 87.8%; *P* = 0.97) and freedom from major cardiovascular events (77.2% versus 75.9%; *P* = 0.70) did not differ significantly between the revascularization group and the intensive medical therapy group. Importantly, however, although there was no significant difference in primary endpoints between the revascularization group and medical therapy group in the PCI stratum, the study findings did demonstrate that the coronary artery bypass grafting (CABG) stratum had a significantly lower rate of major cardiovascular events in the revascularization group (22.4%) than in the medical therapy group (30.5%), which was driven largely by a significant reduction in recurrent MI. Therefore, the CABG cohort, which included a higher-risk population of patients with more extensive multivessel coronary disease, did reveal a lower rate of the secondary endpoint of major cardiovascular events (death, MI, or stroke) compared with intensive medical therapy alone (22.4% versus 30.5%; *P* = 0.01). In essence, the results of the BARI-2D trial in CAD patients with diabetes replicated the principal findings of the COURAGE trial, and reaffirmed that survival rates did not differ with intensive or OMT compared with percutaneous revascularization.

In light of the BARI-2D trial, the role of CABG surgery as a strategy of revascularization was further evaluated in 1212 patients with CAD and heart failure in the...
STICH trial [8], in which patients were randomly assigned to medical therapy alone or medical therapy plus CABG. There was no significant difference in the primary outcome of death from any cause that occurred in 244 patients (41%) in the medical therapy group and 218 (36%) in the CABG group (HR with CABG of 0.86, 95% CI 0.72 to 1.04; \( P = 0.12 \)). However, death from any cause or hospitalization for cardiovascular causes occurred in 411 patients (68%) in the medical therapy group and 351 (58%) in the CABG group (HR with CABG 0.74; 95% CI 0.64 to 0.85; \( P < 0.001 \)). Patients assigned to CABG had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes. In summary, the STICH trial data further support similar outcomes derived from comparisons of PCI as a revascularization strategy to medical therapy (COURAGE) and PCI or CABG versus medical therapy (BARI-2D).

More recently, Hannan et al [9] published an analysis of long-term (2–4 years) comparative outcomes in patients with stable CAD who did and did not undergo PCI from the large, prospective New York State PCI registry. Overall, a total of 9586 patients was followed prospectively in this registry, of whom 89% received PCI, 2% underwent bypass surgery and only 11% received what the authors labeled as “routine medical therapy” (RMT). Outcomes of interest for this study were the composite of death or MI, death alone, MI alone and the rate of subsequent revascularization during follow-up (median 2.87 years). Because so few patients (n = 1100) received RMT alone, the propensity matching comprised only 933 matched pairs of patients (n = 1866), but the study did show that compared with those who received RMT alone, patients who received PCI plus RMT had a significantly lower rate of death or MI (\( P = 0.003 \)), mortality (\( P = 0.02 \)), MI (\( P = 0.007 \)) and subsequent revascularization (\( P = 0.005 \)).

The main confounder in the Hannan study is that this was an observational study in which treatment assignment (PCI or RMT) was not randomized but was rather left to the discretion of the treating cardiologist and, furthermore, the intensity or specifics of medical therapy were not collected to characterize the intensity of pharmacologic therapy. While it can be argued that this represents a more “real world” comparison of revascularization with medical therapy, there was a high likelihood of selection bias and other confounding factors that cannot be entirely eliminated with propensity matching. As such, these findings cannot be considered in any way definitive as the study related to purported significant improvements in clinical outcomes with PCI.

Finally, the effectiveness of revascularization in SIHD was most recently studied in the FAME 2 trial, which was published in 2012 following the original FAME 1 trial of 2009, which evaluated fractional flow reserve (FFR) versus angiography to guide PCI [10,11]. FAME 2 sought to determine whether PCI plus “best available medical therapy” (eg. evidence-based multifaceted medical therapy) would be superior to the best available medical therapy alone as a preferred initial treatment strategy for patients with chronic stable angina – a population very similar to that of COURAGE and BARI-2D. The trial used FFR measurements to evaluate all visually assessed coronary stenoses and, in patients whose FFR values were 0.8 or less, subjects were randomly assigned to an FFR-guided PCI strategy plus best available medical therapy or to a strategy of best available medical therapy alone. The trial was terminated prematurely, 17 months earlier than planned, after the enrollment of 1220 patients (only 888 patients from a projected sample size of 1632), who were randomly assigned to the two strategies, while those patients whose FFR values were greater than 0.8 (n = 332) were enrolled in a parallel registry. The primary outcome measure for FAME 2 was cardiovascular mortality, non-fatal MI, or hospitalization for unplanned revascularization for suspected ACS. There was a significant between-group difference in the percentage of patients who had a primary endpoint with PCI versus medical therapy (4.3% versus 12.7%, HR 0.32, 95% CI 0.19 to 0.53; \( P < 0.002 \)), which was driven solely by a lower rate of urgent revascularization in the PCI group than in the medical therapy group (1.6% versus 11.1% with HR of 0.13 and 95% CI of 0.06 to 0.30; \( P < 0.001 \)). Of note, there were only 33 “hard events”, of which there were only four deaths (three in the OMT arm and one in the PCI arm) along with 29 MIs (14 in the OMT arm and 15 in the PCI arm). Most importantly, the urgent revascularization endpoint that was responsible for the overall primary endpoint was largely a clinical one, and did not mandate objective evidence of either electrocardiographic ischemia or elevated cardiac biomarkers in order to meet this endpoint. Approximately half of...
the 56 unplanned hospitalizations, which led to urgent revascularization, were not accompanied by any objective findings of high-risk ischemia or positive biomarkers.

Therefore, because this was an unblinded trial, there was a potential for selection bias that could have created a lower threshold to admit a trial patient in the OMT arm who had recurrent angina and no objective evidence of ischemia, without first attempting to uptitrate or intensify medical therapy by either increasing the doses of existing medications or adding additional anti-anginal pharmacological agents to delay or obviate the potential need for revascularization. Finally, the FAME 2 trial study population was not particularly high risk as, according to the published baseline characteristics, 11% of patients were asymptomatic, 16% had silent ischemia and 66% has class 1 or 2 anginal symptoms, while only 3% of patients had three-vessel CAD by FFR, with a majority of patients having single-vessel CAD. In addition, the short follow-up period of approximately 7 months probably did not allow for restenosis to emerge in the PCI subset, which might have altered the rate of unplanned revascularization in the PCI arm had the study been continued to the planned end of follow-up. In summary, while FAME 2 did show that an FFR-guided PCI strategy resulted in a lower rate of unplanned revascularizations as compared with medical therapy alone, the notable limitations of the trial as highlighted above makes it difficult to justify or generalize the more widespread use of an FFR-guided revascularization approach in the management of SIHD patients.

Taken together, the COURAGE, BARI-2D, STICH and FAME 2 randomized trials, along with other observational analyses and meta-analyses, have challenged the notion that revascularization is superior to OMT, and clearly more prospectively acquired data are necessary to elucidate further what role revascularization should play in this chronic stable angina population. The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial (ISCHEMIA; ClinicalTrials.gov, NCT 01471522), funded by the US National Institutes of Health, is currently underway and is designed and powered to evaluate the long-term superiority of revascularization of choice combined with OMT versus OMT alone, with respect to cardiovascular death or MI (combined primary endpoint) in patients with stable CAD and moderate to severe myocardial ischemia as assessed by non-invasive stress imaging studies (myocardial perfusion imaging, stress echocardiography, or magnetic resonance imaging). The study is projected to enroll 8000 patients from among 400 sites worldwide, with a planned average follow-up period of 4 years [12].

In summary, clinical trials data firmly support the premise that “revascularization works” in high-risk patients, and is currently the preferred treatment approach (with a class I recommendation) in both STEMI and ACS patients to improve both short and long-term clinical benefit as well as prognostic improvement. The role of PCI and/or CABG surgery is established to lower both incident MI and death rates in these patient populations. The more difficult question of whether “revascularization works” in patients with chronic stable angina and SIHD, based on the clinical trials reviewed above, suggest that OMT should be considered as an initial approach in these patients compared with a “PCI first” treatment strategy. Clearly, further study is warranted to clarify whether patients with moderate to severe pre-treatment myocardial ischemia may fare better with myocardial revascularization compared with OMT alone, as is being tested actively in the ongoing ISCHEMIA trial. Until the results of this large-scale trial are available, we should utilize a judicious and selective approach to decision-making.

Clearly, revascularization is of clinical benefit in selected patient populations when there is a reduction in mortality and/or an improvement in quality of life via a reduction in angina, and should therefore be regarded as the initial management strategy in STEMI and high-risk ACS populations. By contrast, in SIHD patients, evidence derived from multiple, prospective RCTs comparing PCI with OMT shows no incremental benefit on clinical event reduction compared with OMT alone. For this reason, OMT should be considered the foundation of treatment and first-line therapy, unless the severity of anginal symptoms limits the effectiveness of medical therapy or the patient’s quality of life is sufficiently compromised that revascularization should be considered.

References


Imaging myocardial edema

Declan P. O’Regan1 and Stuart A. Cook1,2, 1Robert Steiner MRI Unit, MRC Clinical Sciences Centre, Imperial College London, Hammersmith Hospital Campus, London, UK, 2National Heart Centre Singapore, Singapore

Correspondence: Declan O’Regan, Robert Steiner MRI Unit, MRC Clinical Sciences Centre, Imperial College London, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN, UK Tel: +44 (0)20 3313 1510, e-mail: declan.oregan@imperial.ac.uk

Abstract
Cardiac magnetic resonance (CMR) imaging offers a powerful noninvasive technique for assessing the effects of ischemia–reperfusion injury in the context of acute coronary syndrome (ACS). T2-weighted CMR sequences performed after coronary occlusion accurately identify regions of myocardial edema downstream of the obstructed vessel that enables retrospective determination of the area at risk. Comparing the area at risk with gadolinium-enhanced infarct sizing provides an important tool for clinical decision making and research as it defines the degree of heart muscle salvage following an ischemic injury. The currently available techniques for assessing myocardial edema in ACS are described in this review with an overview of how these inform our understanding of myocardial salvage following primary coronary intervention.

Keywords: Acute myocardial infarction; cardiovascular magnetic resonance; myocardial salvage

Introduction
Acute coronary syndrome (ACS) may rapidly lead to myocardial hypoxia and ischemia within the territory of the occluded vessel. Cardiac magnetic resonance (CMR) imaging provides a powerful tool for defining the extent of ischemia by using T2-weighted imaging to detect tissue edema. This approach reveals the potential infarct size, which is a key parameter in evaluating therapies that aim to maximize myocardial salvage. Reperfusion injury is a major contributor to final infarct size and T2-weighted imaging plays an emerging role in the characterization of reperfusion hemorrhage following revascularization. T2-weighted imaging also has a clinical application in differentiating acute from chronic infarctions and in investigating inflammatory conditions that mimic ACS.

What does T2-weighted imaging show?
T2 relaxation of the magnetic resonance signal is caused by the dephasing of magnetic spins [1]. T2 decay varies between different tissues, and by increasing the echo time image contrast becomes progressively more T2-weighted. Contrast can be further improved by combining fat suppression techniques such as short TI inversion recovery with dual inversion black blood imaging to null the magnetization of blood in the imaging slice [2]. The signal intensity in T2-weighted imaging is very sensitive to changes in mobile water content, which increases during acute ischemia as a result of intracellular sodium accumulation [3] and cell swelling [4]. CMR using T2-weighted sequences provides the optimal technique for quantifying acute myocardial edema in the aftermath of ACS, and offers an important insight into the effects of therapy on ischemia–reperfusion injury.
Assessing myocardial salvage

Maximizing myocardial viability during ST elevation myocardial infarction (STEMI) is the principal means by which patients benefit from coronary reperfusion [5, 6]. Time to reperfusion is critically important as a wave front of irreversible ischemic injury progressively advances throughout the area at risk in the territory of the infarct-related artery [7, 8]. As tissue perfusion is re-established there is the potential for salvaging viable myocytes leading to recovery of contractile function within transiently ischemic myocardium [9]. Myocardial salvage represents the difference between the potential infarct size and the final infarct size, which is a key concept because its measurement can be used to develop strategies to optimize the management of acute myocardial infarction [10]. Edema within acutely ischemic myocardium is manifested by a zone of hyper-intensity on T2-weighted imaging, which develops within the first hour of coronary occlusion (Fig. 1) [11]. This zone on T2-weighted imaging closely corresponds to the ischemic territory determined with fluorescent microspheres [12] and perfusion single-photon emission computed tomography [13].

Preclinical research has shown that this zone includes both reversibly and irreversibly injured myocardium within reperfused sub-endocardial infarctions [14]. The size of the ischemic vascular bed depends on the anatomical boundaries of the occluded coronary artery, but the extent of necrosis within that zone is variable and may be arrested by timely coronary reperfusion [15]. Late gadolinium enhancement (LGE) defines the final infarct size as a region of hyperintense necrosis [16]. Combining the two techniques of T2-weighted imaging and LGE enables reversibly injured myocardium to be distinguished from ischemic but potentially viable myocardium [17]. The resulting myocardial salvage index provides an important parameter for assessing the effectiveness of reperfusion after primary percutaneous coronary intervention (PPCI).

Primary endpoints in the clinical evaluations of reperfusion therapy, such as death or major adverse cardiac events, have a low incidence in short-term follow-up. Using salvage as a surrogate endpoint of clinical trials in STEMI provides immediate biological data on the effect of treatment that also controls for variations in the size of the area at risk [18, 19]. Although the use of CMR endpoints in STEMI has been criticized for a lack of validation studies [20] recent data support the use of myocardial salvage as an endpoint for clinical trials investigating novel reperfusion strategies that outperform the assessment of infarct size alone [21, 22].

A range of signal intensity thresholds has been used to quantify the area at risk on T2-weighted images, and as yet there is no consensus on which of these offers the most accurate or reliable approach [13, 17, 22, 23]. More sophisticated segmentation techniques have shown promise for semi-automated image analysis and direct parametric mapping of signal relaxation, which has recently been used to map the T2 decay constants throughout the left ventricle after STEMI [23–26]. For salvage measurement and assessment of the peri-infarct border zone careful co-registration between T2-weighted imaging and LGE is also necessary [27]. The extent of hyperintensity on T2-weighted images appears stable during the first week after infarction before declining over the subsequent 6 months so there is a window of opportunity to assess the area at risk [28, 29]. However, it has been suggested that the extent of myocardial edema shown on T2-weighted imaging may be influenced by reperfusion injury extending beyond the infarct margins [30]. In contrast, the extent of LGE is dynamically evolving during the first week after reperfusion, so quantification of infarct size is critical in the interval after PPCI [29, 31, 32]. Hemorrhage within the infarct opposes the effect of high-signal edema and this may lead to a substantial underestimate of the area at risk in

![Fig. 1](image)

**Fig. 1** Black blood T2-weighted image in the left ventricular short axis of a patient 24 hours following coronary intervention for acute myocardial infarction. Extensive high-signal edema is present throughout the lateral wall.
more extensive infarcts [23]. Salvage measurement is therefore not straightforward but is achievable with the right expertise and suitable software tools (Fig. 2).

**Reperfusion hemorrhage**

Prompt restoration of myocardial perfusion is the most important goal of PPCI in treating STEMI patients; however, despite re-establishing patency of the infarct-related coronary artery, achieving optimal tissue perfusion and myocyte salvage in all patients has remained elusive [33, 34]. The process of restoring blood flow to ischemic tissue can itself induce myocyte damage and this phenomenon, known as ischemia–reperfusion injury, can paradoxically reduce the beneficial effects of myocardial reperfusion [35]. This process results in the death of cardiac myocytes that were viable immediately before myocardial reperfusion and may be responsible for up to half the final infarct size [36]. Interstitial hemorrhage occurs within severely ischemic myocardium during reperfusion, and provides a potential means for identifying reperfusion injury with imaging [37, 38]. Blood products have paramagnetic properties that cause signal loss within the zone of edema on spin-echo T2-weighted images [23, 39]. T2*-weighted gradient-echo imaging provides an even more sensitive technique for detecting iron, and allows the extent of reperfusion hemorrhage to be quantified (Fig. 3) [40, 41]. CMR studies have shown that hemorrhage is a frequent complication after apparently successful coronary intervention, and is an independent predictor of adverse ventricular remodeling regardless of the initial infarct size [42].

**Mimics of acute coronary syndrome**

T2-weighted imaging enables acute ischemia to be distinguished from chronic infarction, and can be a valuable tool in the investigation of patients with multivessel disease as it is able to define the area at risk even in the absence of infarction, which can then be used to direct interventional strategies to the culprit artery [43].

The diagnosis of acute myocarditis may be difficult because of the nonspecific clinical features, and CMR provides an accurate method for diagnosis [44]. In the context of myocarditis there is edema and usually some fibrosis that is most commonly localized to the basal lateral and inferolateral walls. Although the distribution of edema is often focal and coincides with the zone of LGE (Fig. 4) [45], it is often diffuse and measurement of the signal intensity ratio between myocardium and skeletal muscle is often required [46].
Stress-induced (takotsubo) cardiomyopathy is typically manifested by transitory apical (or mid-ventricular) dyskinesia in the absence of significant coronary artery disease [47]. CMR demonstrates the characteristic wall motion abnormality and the absence of an infarct as the basis for the new diagnosis of takotsubo cardiomyopathy [47]. T2-weighted imaging provides diagnostic and prognostic information in the evaluation of acute chest pain [48]. Conclusions

T2-weighted imaging enables acute inflammation, including that observed throughout ischemic myocardium, to be diagnosed and quantified. It plays a crucial role in determining the success of reperfusion therapies by showing the potential infarct size as it was before coronary intervention. Hemorrhage on T2-weighted images may also be observed in hypertrophic cardiomyopathy and cardiac sarcoidosis, which may reflect underlying focal ischemia and inflammation, respectively [49, 50].

References


7. Reimer KA, Jennings RB (1979) The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 40:633–644


Angiogenic therapy: is it still viable?

Christian Seiler, Cardiology, University Hospital, Bern, Switzerland

Correspondence: Christian Seiler, Professor and Co-chairman of Cardiology, University Hospital, Freiburgstrasse, CH-3010 Bern, Switzerland
Tel: + 41 31 632 36 93, fax: +41 31 632 42 99
e-mail: christian.seiler@insel.ch

Abstract
Coronary collateral vessels are an alternative source of blood supply to myocardium jeopardized by ischemia. Well-developed coronary collateral arteries in patients with coronary artery disease (CAD) mitigate myocardial infarcts and improve survival. Coronary collateral flow can be assessed only during vascular occlusion of the collateral-receiving artery. The reference for coronary collateral assessment is the measurement of the intracoronary occlusive pressure-derived collateral flow index (CFI) expressing collateral flow as a fraction of flow during vessel patency. Approximately one out of five patients with CAD cannot be revascularized by percutaneous coronary intervention or coronary artery bypass grafting. Therapeutic promotion of collateral growth is a valuable treatment strategy in those patients. Promotion of collateral growth should aim at inducing the development of large conductive collateral arteries (ie, arteriogenesis) rather than the sprouting of capillary-like vessels (ie, angiogenesis). Collateral function expressed as CFI, and thus arteriogenesis, is effectively promoted by the activation of monocytes/macrophages by means of granulocyte colony-stimulating factor or of augmenting coronary arterial shear force.

Keywords: Angiogenesis; arteriogenesis; collateral circulation; coronary circulation

Introduction
Cardiovascular diseases are the leading cause of death in industrialized countries. In Europe, annual mortality from all causes in the general population amounts to approximately one per 100 inhabitants, one person out of 200 dies from cardiovascular disease, and one out of 300 experiences CAD and its consequences. Established options for revascularization in CAD include angioplasty and surgical bypass, both of which are not suitable in approximately one out of five patients in whom the extent of coronary atherosclerosis is especially severe. In such patients, an alternative treatment strategy to revascularization is warranted both to control symptoms as well as to alter the course of advanced CAD. An ideal candidate to fill this therapeutic gap is the promotion of coronary collateral growth, ie, the induction of natural bypasses.

In this context, the question given in this paper’s title on the viability of angiogenic therapy is vital. This review aims to outline the reasons for its lack of efficacy in the clinical setting, and to provide evidence for the usefulness of a conceptually more sound and thriving strategy for collateral structural promotion, that is, arteriogenesis.

Relevance of the coronary collateral circulation
The coronary collateral circulation has been recognized for a long time as an alternative source of blood supply to an ischemic myocardial area. More than 200 years ago, Heberden [1] described...
a patient who had been nearly cured of his angina pectoris by sawing wood each day, a phenomenon called warm-up or first effort angina, which was traditionally ascribed to coronary vasodilation with opening of collateral vessels. There have been numerous investigations demonstrating a protective role of warm-up, versus poorly developed collateral arteries resulting in smaller myocardial infarcts [2], less ventricular aneurysm formation, improved ventricular function [2], fewer future cardiovascular events [3] and improved survival [4]. However, the functional relevance of coronary collateral vessels in humans has also been a matter of debate for many years [5]. Much of this controversy was probably due to inadequate means for gauging human coronary collateral function and to the investigation of populations too small to be representative of all the patients with CAD. In the absence of stenoses, it has been traditionally assumed that coronary arteries are functional end-arteries. Using direct and quantitative intracoronary collateral measurements (Fig. 1), it has, however, been documented that the notion of the human coronary circulation being built without preformed functioning anastomoses between vascular territories is a myth rather than reality. In the absence of obstructive CAD or even in entirely normal hearts, there is collateral flow to a briefly occluded coronary artery sufficient to prevent ECG signs of myocardial ischemia in one fifth to one fourth of the population studied [6]. In the context of therapeutically promoting the function of collaterals, the existence of such pre-formed anastomoses is crucial.

**Therapeutic promotion**
Therapeutic angiogenesis/arteriogenesis are strategies for revascularizing ischemic myocardial tissue by the formation/remodeling of “natural bypasses”, ie, collateral vessels. Understanding the basic steps and regulatory mechanisms of angiogenesis is important for designing such strategies.

**Vasculogenesis**
The initial steps for the formation of the vascular system during embryonic life involve the differentiation of mesodermal cells into angioblasts that give rise to endothelial cells forming the first primitive blood vessels [7].

**Angiogenesis**
New vessels can subsequently develop from the pre-existing plexus by sprouting and intussusception. This formation of new vessels has been called angiogenesis [8]. In addition to endothelial cells, pericytes (for capillaries) and smooth muscle cells (for larger vessels) are necessary for the maturation of these newly growing vessels [8]. Angiogenesis and arteriogenesis are not restricted to the growing organism. Tissue repair and regeneration, eg, wound healing and the cyclic changes of the female reproductive system, are manifestations of angiogenesis. New capillaries form around zones of tissue ischemia, as occurs in myocardial infarction and stroke. In the context of ischemia with hypoxia, growth factors such as hypoxia-inducible factor 1α and inflammatory mediators are

![Fig. 1](image-url) Invasive measurement of coronary collateral flow index (CFI) by simultaneous recording of mean and phasic aortic pressure ($P_{ao}$), distal coronary occlusive pressure ($P_{occl}$) and central venous pressure (CVP). In addition, an intracoronary (ic) ECG is obtained during the 2-minute coronary occlusion.
released locally, leading to vasodilation, enhanced vascular permeability and the accumulation of monocytes and macrophages, which in turn secrete more growth factors and inflammatory mediators [9] (Fig. 2). These inflammatory cells release metalloproteinases that dissolve the surrounding matrix and the basal membrane of the preformed vessel. Hypoxia sensitizes the local endothelial cells to the chemotactic and proliferative effects of various growth factors by upregulating their receptors. Endothelial cells detach from their neighbors, migrate, proliferate and subsequently form a new vessel with a lumen. Pericytes and smooth muscle cells are also involved in this process.

**Arteriogenesis**

Invasive cardiologists have long been aware of the occurrence of large epicardial branch or septal collateral vessels after total or subtotal occlusion of a major coronary artery. These usually become visible within 2 weeks following an occlusion, and they arise from preformed collaterals. The remodeling process involved in this structural recruitment of already existing collateral vessels has been termed arteriogenesis [9, 10]. Large bridging collaterals are physically much more effective in salvaging ischemic myocardium than small peri-ischemia, ie, “angiogenic” capillaries. The complete obstruction of a coronary artery leads to a fall in post-stenotic pressure and to a redistribution of blood to pre-existing, anastomotic arterioles originating from the nonischemic vascular region. The resulting longitudinal shear forces lead to an increased expression of certain endothelial chemokines, adhesion molecules and growth factors (Fig. 2). Within days, circulating monocytes attach to the endothelium of the bridging collateral vessels causing a local inflammatory reaction [9]. Matrix dissolution occurs and the vessels undergo a growth process with active proliferation of their endothelial and smooth muscle cells.

**Growth factor candidates**

A variety of physiological molecules has been identified that appear to promote angiogenesis. Most act by stimulating the migration and proliferation of endothelial cells and/or smooth muscle cells, like the family of fibroblast growth factors (FGF) and vascular endothelial growth factors (VEGF). Both cause vasodilation by stimulating the release of nitric oxide. It is, therefore, important in animal and clinical studies to differentiate between improved perfusion caused by mere vasodilation and true collateral growth. Other growth factor candidates include placental growth factor, angiopoietin 1, transforming growth factor β, platelet-derived growth factor and about half a dozen other cytokines, proteases and proteins [11,12]. Arteriogenesis has been shown to be induced by activated macrophages [13], by lipopolysaccharide [9], monocyte chemotactic protein 1 [10], tumor necrosis factor α, FGF and also via granulocyte macrophage colony-stimulating factor (recombinant human GM-CSF; Molgramostim) [14].

**Clinical studies**

Angiogenesis may be induced by various promoters, such as VEGF and FGF, angiogenic agents most often used in current clinical studies [15, 16]. Although animal studies have established the principle that collateral function improves after delivering angiogenic growth factors [17], and although the first uncontrolled clinical studies have demonstrated the safety and feasibility of VEGF and basic FGF [18], efficacy data on angiogenic therapy have been scarce. The largest controlled clinical trials using VEGF165 (Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis; VIVA [19]) and FGF2 (Fibroblast Growth Factor Initiating Revascularization Trial; FIRST [20]) in 178 and in 337 patients with CAD, respectively, have not shown an effect on the study endpoints treadmill
exercise time, angina pectoris at 60 and 120 days (VIVA) and, respectively, exercise tolerance test duration at 90-day follow-up and changes in the magnitude of myocardial ischemia by Tc99m single photon emission computed tomography. Negative results of angiogenic growth factors in promoting coronary collaterals have probably been due to the use of endpoints for their assessment that have been too blunt to discern subtle changes in collateral function. At this phase of clinical angio/arteriogenic therapy, during which screening for the most effective growth factor among more than a dozen candidates has not even properly begun, selection of the best agents ought to be based on accurate and direct invasive measurements of coronary collateral flow. Equally important, angiogenic factors may have been employed that induce the formation of small, high resistance capillaries (angiogenesis) rather than the large interconnecting arterioles (arteriogenesis) that are required for the salvage of myocardium in the presence of occlusive CAD. In two randomized placebo-controlled clinical trials, GM-CSF has been shown to be effective with regard to sequentially and invasively obtained collateral flow in patients with CAD [21, 22]. However, GM-CSF appears to be related to atherosclerotic plaque rupture and can, therefore, not be regarded as safe in the treatment of patients with CAD [22]. Granulocyte colony-stimulating factor has recently been shown to be effective in the promotion of collateral function in a controlled randomized trial among 52 patients undergoing baseline and follow-up collateral flow index (CFI) measurements (Fig. 3) [23].

Arteriogenesis is related to enhanced tangential shear forces at the vessel wall in response to increased flow through pre-existing collateral connections (Fig. 2). Therefore and aside from the biochemical stimulation of monocytes/macrophages, physical exercise would be a therapeutic option for inducing arteriogenesis, because cardiac output and thus coronary flow is elevated along the arterial branches of the coronary circulation during exercise. So far, a prospective investigation in humans on the effect of exercise regarding collateral growth has employed an insensitive instrument for collateral assessment, ie, angiographic imaging of spontaneously visible collateral vessels, and has had negative results [24]. Data from our own laboratory suggest that even in the absence of CAD, collateral flow as assessed by intracoronary pressure-derived measurements is augmented substantially in response to endurance exercise training [25]. Also, a study in CAD patients participating in a 3-month rehabilitation programme has shown improved collateral function in comparison to a sedentary control group [26].

An alternative mechanism to physical exercise of applying augmented vascular shear forces is based on external counterpulsation (ECP), which is synchronized to the ECG and executed during diastole. Encouragingly, the first controlled trial in a group of CAD patients undergoing a 30-hour programme of high-pressure ECP (300 mm Hg) and in a group undergoing sham ECP at 80 mm Hg inflation pressure has recently revealed an unexpectedly high increase in CFI between baseline and follow-up at 4 weeks (Fig. 4) [27].
Individual changes of collateral flow index (CFI; vertical axis) from baseline to follow-up measurement in response to external counterpulsation (ECP; left) and to sham ECP (right).

Fig. 4

Conclusions
Therapeutic promotion of collateral growth is a valuable treatment strategy for patients with CAD. The promotion of collateral growth should aim at inducing the development of large conductive collateral arteries (ie, arteriogenesis) rather than the sprouting of capillary-like vessels (ie, angiogenesis). Collateral function is effectively promoted via the activation of monocytes/macrophages by means of granulocyte colony-stimulating factor or of augmenting coronary arterial shear force.

Acknowledgments
This study was supported by grants from the Swiss National Science Foundation for Research, grant no. 32003B_141030/1 and the Swiss Heart Foundation.

References
Metabolic cardiac protection is beneficial in patients undergoing coronary revascularization: is it necessary afterwards?

Yury Lopatin, Volgograd Medical State University, Volgograd Regional Cardiology Centre, Volgograd, Russia

Correspondence: Yury Lopatin, Professor and head of Cardiology Department, Volgograd Regional Cardiology Centre, 106, Universitetsky pr., Volgograd, Russia
Tel: +7 8442 415623 e-mail: yu.lopatin@gmail.com

Abstract
Coronary revascularization procedures (coronary artery bypass grafting and percutaneous coronary intervention) take their place among the principal approaches to coronary artery disease (CAD) treatment. These procedures not only successfully alleviate the symptoms of the disease, but may also improve outcome in subsets of CAD patients. However, accumulating data suggest the possibility that myocardial injury develops as a response to the restoration of coronary blood flow. This paper describes the potential benefits of trimetazidine as a promising agent for cardiac protection in patients undergoing coronary revascularization. The rationale for long-term treatment with trimetazidine after coronary revascularization procedures is also discussed.

Keywords: coronary artery bypass grafting (CABG); metabolic cardioprotection; percutaneous coronary intervention (PCI); trimetazidine

Introduction
The history of the use of coronary revascularization procedures – coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI) – extends back half a century. Over this period, the two strategies of coronary revascularization have undergone serious technical advances and take their place among the principal approaches to coronary artery disease (CAD) treatment. Indeed, both CABG and PCI not only successfully alleviate the symptoms of the disease, but can also improve outcome in subsets of CAD patients (ie, those with left main CAD, proximal stenoses of the left anterior descending (LAD) artery or two to three-vessel coronary disease with left ventricular dysfunction) [1].

In recent years, there have been active discussions about the benefits of drug-eluting stents, arterial grafts, off-pump CABG, as well as hybrid operations [2–4]. Moreover, convincing evidence has been obtained in favour of the use of optimal medical treatment in CAD patients, which includes rational combination of intensive lifestyle interventions and pharmacological management [5,6]. In this setting, the choice of the most preferable method (or methods) for the
treatment of CAD patients implies that the maximal benefit is gained from each strategy used, irrespective of whether it is invasive or not. Therefore, the decision-making behind the choice of a particular procedure for coronary revascularization, especially in patients with multivessel disease, necessitates active communication between cardiologists and cardiac surgeons, and other experts, if required. This principal position was highlighted in the European guidelines on myocardial revascularization updated in 2010 [1].

It is interesting that from the beginning of the era of myocardial revascularization in CAD patients, the data began to accumulate about the development of myocardial lesions in response to the restoration of coronary blood flow after an ischemic episode. Myocardial reperfusion injury was first described for the first time in 1960 by Jennings et al [7]. The authors observed cell swelling, contracture of myofibrils, disruption of sarclemma, and the appearance of intramitochondrial calcium phosphate particles in reperfused ischemic canine myocardium. In 1977, Bulkely and Hutchins [8], in a study of myocardium in 58 patients after CABG (all patients died within 1 month after the intervention), reported for the first time the paradox of myocardial lesion development despite successful coronary revascularization. This paradox was called “ischemia-reperfusion injury”, and its occurrence and development is profoundly influenced by the formation of reactive oxygen species (such as superoxide anion [\( \bullet \text{O}_2^- \)], hydroxyl radical [\( \bullet \text{OH} \)] and hydrogen peroxide [\( \text{H}_2\text{O}_2 \)]) in response to reperfusion of ischemic myocardium, which leads to cardiomyocyte calcium overload and, eventually, to the injury and death of heart cells.

The development of ischemia-reperfusion injury was shown to be associated with an aggregation and activation of leukocytes, aggregation of platelets, activation of apoptosis, cardiotoxic effect of angiotensin II, and activation of the complement system [9–11]. The above stated disorders can manifest not only as the “no-reflow” phenomenon, microvascular and endothelial dysfunction, myocardium stunning, reperfusion arrhythmias, but also as irreversible myocardial reperfusion injury.

Of note is the fact that periprocedural myocardial injury is not a rare observation. For example, Ioannidis et al [12] have shown that approximately one-third of all elective PCI procedures are associated with severe myocardial injury, which has been linked with higher subsequent mortality. Is it possible to prevent potential cardiomyocyte death occurring at the restoration of coronary blood flow?

**Does the administration of trimetazidine represent a promising method of cardioprotection in patients undergoing PCI and CABG?**

One of the promising methods for cardioprotection in patients undergoing PCI and CABG is the administration of trimetazidine. Trimetazidine is known to exert its anti-ischemic effect by the selective inhibition of long-chain 3-ketoacyl-CoA thiolase and direct stimulation of pyruvate dehydrogenase, which provides a shift in cardiac energy metabolism from fatty acid oxidation to glucose oxidation. As a result, trimetazidine preserves the necessary ATP level in cardiomyocytes, promotes a decrease in intracellular acidosis and prevents intracellular calcium overload. It reduces the myocardial injury caused by free radicals and, therefore, modulates the inflammatory response and can limit the necrotic area of myocardium. This effect becomes especially useful in the reperfusion period, when because of the restoration of oxidized blood inflow to the previously ischemic areas of myocardium, fatty acid β-oxidation is increasing sharply, and pyruvate (formed from glucose or lactate) oxidation is paradoxically decreasing. Experimental studies have shown that trimetazidine in the settings of ischemia-reperfusion prevents a sharp increase in the permeability of mitochondrial membranes, reduces the activation of neutrophils, as well as decreasing the rate of apoptosis of cardiomyocytes [13–16].

Several randomized clinical trials (RCT) have demonstrated that the administration of trimetazidine before PCI or CABG is associated with more rapid normalization of the ST-segment on the surface ECG, lower levels of oxidative stress markers (lactate, malondialdehyde) and myocardial necrosis markers (troponin, creatine phosphokinase [CPK], creatine phosphokinase myocardial type [CPK-MB]) in the postoperative period.

The first RCT on this issue was a double blind, placebo controlled study performed by Kobert et al [17], in which 20 patients with CAD and LAD artery disease received intracoronary trimetazidine solution (6 mg) or placebo during PCI. The authors found that trimetazidine solution, compared to placebo, provides a significantly earlier recovery of ST-segment to the isoelectric
line and in T wave changes during the repeated balloon inflations, without altering hemodynamic parameters.

In another RCT, called LIST [18], patients also received trimetazidine in solution form. This prospective, double blind, placebo controlled study included 94 patients with acute myocardial infarction, who were treated with trimetazidine intramuscularly (40 mg bolus for 2 minutes, and then 60 mg daily in the form of constant infusion for 48 hours) before primary PCI on the infarct-related artery.

That RCT has also shown more rapid resolution of ST-segment change in patients treated with trimetazidine solution compared with placebo.

The results of these two RCT, which used trimetazidine solution, should be considered primarily as the rationale for trimetazidine administration before PCI. However, there are data that demonstrate a positive effect of trimetazidine administered in oral form before PCI.

In the open, controlled RCT of Polonski et al [19], which included 44 patients with one-vessel disease (stenosis >70% in the middle of the LAD artery), trimetazidine was administered from at least day 4 before PCI. The authors found that trimetazidine treatment resulted in a significantly lower ST-segment elevation during PCI. In addition, the mean values of ST-segment elevation during all the balloon inflations were lower in the trimetazidine group (1.66 ± 1.50 mm versus 3.29 ± 1.59 mm in the comparison group; \( P = 0.001 \)). Moreover, trimetazidine significantly increased the time from balloon inflation to angina occurrence (50 ± 26.2 seconds versus 32 ± 15.0 seconds in the comparison group; \( P = 0.03 \)) and, accordingly, decreased the time from balloon deflation to the disappearance of pain (19.3 ± 11.4 seconds versus 40.1 ± 16.8 seconds in the comparison group; \( P = 0.001 \)).

The study of Bonello et al [20] included 206 stable angina patients with one-vessel coronary disease. Half of the patients received trimetazidine in the single loading dose of two tablets daily at 30 minutes before PCI. The primary endpoint was the maximal level of troponin I, which is the marker of irreversible myocardial injury. Troponin I levels were measured before PCI, as well as at 6, 12, 18 and 24 hours after PCI. The trimetazidine intake in a single dose was associated with a significant reduction in the troponin I level, compared to the control group, at all the time points after PCI (mean value and SD: at 6 hours – 4.2 (0.8) versus 1.7 (0.2), \( P < 0.001 \); at 12 hours – 5.5 (1.5) versus 2.3 (0.4), \( P < 0.001 \); at 18 hours – 9 (2.3) versus 3 (0.5), \( P < 0.001 \); and at 24 hours – 3.2 (1.2) versus 1 (0.5), \( P < 0.001 \)).

The results were also positive in studies with trimetazidine administration before CABG.

The double blind, placebo controlled study of Fabiani et al [21] is probably the first study performed in this setting. The participants with scheduled CABG received trimetazidine (60 mg daily) for 3 weeks before surgery. Moreover, the drug was added to the cardioplegic solution (trimetazidine \( 10^{-6} \) M). The measurements of malondialdehyde in the blood from the coronary sinus showed that at 20 minutes after the reperfusion was started, the increase in this marker of oxidative stress was significantly lower in the trimetazidine group (from 1.60 ± 0.11 to 1.79 ± 0.2 mmol/L), compared with the placebo group (from 1.17 ± 0.11 to 2.84 ± 0.58 mmol/L). At 4 hours after the operation, circulating myosin was identified in all the CAD patients from the placebo group and in only half of the patients from the trimetazidine group (\( P = 0.036 \) between groups). These data are consistent with the results of other double blind, placebo controlled studies [22,23], showing that trimetazidine provides a significant (versus placebo) reduction in lactate levels, a reduced requirement for calcium-channel blockers in the period of aortic X-clamp removal, as well as a reduction in the troponin T level.

Is the continuation of trimetazidine treatment still needed after coronary revascularization procedures?

Actually, yes, especially if a CAD patient after the coronary revascularization procedure still experiences angina or has left ventricular systolic dysfunction. The subgroup analysis of the TRIMPOL II study [24] has shown that the addition of trimetazidine, to the therapy of 94 patients who had already undergone PCI or CABG and still experienced angina attacks, resulted in a significant increase in time to 1 mm ST-segment depression, total exercise time, time to angina onset, and total work.

Another example of a positive answer to the above question is the results of the placebo controlled RCT performed by Labrou et al [25]. The study aimed to assess the efficacy of trimetazidine in the prevention
of myocardial injury after PCI, as well as its influence on left ventricular systolic function at 1 and 3 months after the procedure. Compared with placebo, trimetazidine treatment resulted in a significantly greater reduction in troponin I and CPK-MB levels. In particular, at 48 hours after the procedure, the increased troponin I level was found in 15% of patients treated with trimetazidine and 32% of patients who received placebo. At 24 hours after PCI, the increased CPK-MB level (>5 ng/mL) was observed in 22% of patients from the trimetazidine group and 40% of patients from the placebo group.

It is worth mentioning that further intake of trimetazidine resulted in a significant improvement in the regional contractility of left ventricular myocardium, a significant decrease in the number of cases with left ventricular ejection fraction (LVEF) reduction less than 50%. Moreover, trimetazidine therapy was also associated with a significant improvement of the LVEF, compared with placebo, at 1 and 3 months of follow-up.

According to the results of an open prospective randomized study [26], which included 306 patients with multivessel CAD and stable angina (2.9 ± 0.2 Canadian Cardiac Society), heart failure (2.2 ± 0.1 New York Heart Association), left ventricular aneurysm (12% of patients) who were undergoing CABG, the administration of trimetazidine MR at a dose of 70 mg/day for 2 weeks before CABG resulted in a lower CPK-MB level in the early postoperative period, less frequent development of hemodynamically significant cardiac rhythm disorders and intraoperative myocardial infarction. It is noteworthy that further administration of the drug for 3 years led to a significantly higher exercise tolerance and a more pronounced increase in LVEF. Repeated angina pectoris was observed in 12.4% of patients in the reference group and in 7.2% of patients with CAD receiving treatment with trimetazidine MR (Figs 1–3).

LVEF in the group of patients receiving trimetazidine MR increased by 15.3% (from 50.3 ± 1.6% to 52.8 ± 1.1% by the end of the first month, and to 55 ± 0.9% by the end of the follow-up period). In the control group, the changes in this parameter were less significant and accounted for 1.5% (from 51.5 ± 2.1% to 53.5 ± 0.2% by the end of the first month, and to 52.3 ± 1.5% by the end of the observation period). Another open prospective randomized study [27] showed that the prescription of trimetazidine MR at a dose of 70 mg/day for 2 weeks before PCI in 214 patients with multivessel CAD, stable angina (2.7 ± 0.2 Canadian Cardiac Society) and heart failure (2.0 ± 0.1 New York Heart Association) followed by the administration of the drug for 3 years, provided a significant improvement in left ventricular systolic function and exercise tolerance. Arrhythmias as well as episodes of silent myocardial ischemia were found to be less frequent in the trimetazidine MR group, compared to the control group. The rates of hospitalization for acute coronary syndromes were 4.7% in the trimetazidine MR group and 7.5% in the control group.
The rates of repeat coronary revascularization were 9.3% in the trimetazidine MR group and 14.0% in the control group (*P < 0.05) (Fig. 4). 

**Conclusion**

At the present time, the pharmacological modulation of fatty acid oxidation is considered a promising option for the treatment of patients with chronic heart failure, including diastolic heart failure, especially in elderly patients and women [28]. According to the meta-analysis of Gao et al [29], which included 17 trials with pooled data for 955 patients with heart failure, trimetazidine improved systolic function and clinical symptoms. Moreover, these improvements associated with trimetazidine treatment may result in reduced all-cause mortality, fewer cardiovascular events and hospitalizations after long-term treatment. Indeed, large scale, prospectively designed, randomized, double blind trials are still required to clarify the role of trimetazidine in patients undergoing coronary revascularization. First, the most optimal timing and route of trimetazidine administration after the intervention needs to be identified. Also a question remains about the duration of trimetazidine therapy after PCI or CABG. It seems to be completely clear that in the case of CAD patients with persistent angina symptoms or the presence of left ventricular systolic dysfunction, trimetazidine administration will provide additional benefits allowing us to expect a reduction in the risk of adverse cardiac events.

References

Coronary artery disease: two sides of the same coin

Paola Capozza and Giancarlo Todiere, Cardiovascular Medicine Division, Cardiac and Thoracic Department, University of Pisa, Fondazione Toscana "G. Monasterio", Pisa, Italy

Correspondence: Paola Capozza, Cardiovascular Medicine Division, Cardiac and Thoracic Department, University of Pisa, Via Paradisa 2, 56124 Pisa, Italy
Tel: 0039 050 995307, fax: 0039 050 995308
e-mail: paola.cap@alice.it

Abstract
A 48-year-old woman was admitted to our department with a diagnosis of acute coronary syndrome without persistent ST-segment elevation, and coronary angiography showed no significant atherosclerotic lesion, as documented by fractional flow reserve (FFR). On the same day we also admitted a 52-year-old man with chest pain at rest, an ECG showing downsloping ST-segment depression in anterolateral leads and a critical stenosis of a large marginal branch. In this case, FFR was pathologically low but also varied significantly with intracoronary nitrates. These examples demonstrate once again the complexity of ischemic heart disease in the acute setting of coronary syndromes. It is important to approach ischemic heart disease in a multipathological/factorial manner because the mechanisms underlying myocardial ischemia are extremely heterogeneous and do not merely depend on a fixed atherosclerotic coronary artery stenosis.

Keywords: Acute coronary syndrome; coronary angiography; fractional flow reserve

Heart Metab. (2013) 58:31–34

History
Patient 1
A 48-year-old woman was admitted to our department with a diagnosis of unstable angina.

Her cardiovascular risk profile was characterized by mild dyslipidemia and she was a cigar smoker.

In 2007 she underwent a left mastectomy with axillary lymphadenectomy for breast cancer, followed by chemotherapy for liver metastases (at the time of admission there was no evidence of new disease). At 08.00 hours on the day of admission, she had chest pain at rest radiating to arms and upper back, and associated with nausea and vomiting. In the emergency department (ED) she was asymptomatic for chest pain at arrival (11.05 hours). During observation in the ED she had a further episode of chest pain (relieved by sublingual nitrates) with downsloping ST-segment depression in leads V4–V6 (Fig. 1). Cardiac enzymes were negative. At physical examination she had blood pressure 120/75 mm Hg, pulse 75/minute, no heart murmurs, Killip class I. Echocardiography showed normal left ventricular volumes and ejection fraction (59%), without wall motion abnormalities. At coronary angiography a 50% diameter stenosis in the mid left anterior descending coronary artery was found (Fig. 2A); after intracoronary
nitrates the epicardial vessels were dilated and the stenosis disappeared (Fig. 2B). This lesion was not treated with angioplasty because the fractional flow reserve (FFR) was in the normal range (0.88, normal value >0.80) (Fig. 3). The patient started a tailored therapy with nitrates and verapamil and she was free from angina and events during the follow-up.

**Patient 2**

On the same day as patient 1, we admitted to the cardiology unit a 52-year-old man with chest pain at rest. His cardiovascular risk profile was characterized by dyslipidemia, smoking and arterial hypertension. In the past he had a gastric ulcer. He described new onset angina (<2 weeks) with a severe episode on the morning of admission. The ECG in the ED showed sinus rhythm with left anterior hemiblock, while echocardiography showed normal left ventricular volumes and ejection fraction (56%), with hypokinesia of the mid apical segments of the lateral and inferior walls. Troponin I was elevated (12.4 ng/mL) and during the ED stay he had episodes of complete atrioventricular block. In our department he was asymptomatic. On physical examination he had blood pressure 135/85 mm Hg, pulse 60/min, an apical systolic murmur, Killip class I. At coronary angiography a large marginal branch showed an eccentric plaque, determining a critical stenosis of 80–90% (Fig. 4), as documented by FFR (0.67). In this case nitrates allowed only a minimum increase in flow (fractional flow 0.73) with no substantial change in stenosis severity (Fig. 5). The patient underwent percutaneous coronary intervention with stent implantation. He was discharged on double antiplatelet therapy, β-blockers, a high dose of atorvastatin and an angiotensin-converting enzyme inhibitor. He was also free from cardiovascular events at follow-up.

**Discussion**

We have presented two cases of acute coronary syndrome with similar clinical presentations but with very different pathogeneses of ischemia requiring tailored subsequent treatment. Patient 1 had unstable angina...
caused by diffuse coronary spasm, predominantly affecting the left anterior descending artery, but without a classic definite epicardial coronary stenosis. In contrast, a critical fixed stenosis was found in patient 2. Coronary vasomotion can thus be considered the leading pathology underlying the acute coronary syndrome in the first case. While in the second case, a classic plaque with a large atherosclerotic burden was the underlying cause. Therefore, these cases highlight two different pathologies, both leading to regional myocardial ischemia, and near identical presentations. Marzilli et al [1] recently published a review to explain the Copernican revolution, as the authors interpret the paradigm of ischemic heart disease. The solar system of ischemic heart disease puts myocardial ischemia at the center, confining coronary stenosis on the side as one of many contributors to myocardial ischemia.

We know that atherosclerosis, traditionally considered a focal cholesterol storage disease, is now viewed as a widespread inflammatory process, responsible for the development, evolution and complications of arterial lesions [2, 3]. It is now recognized that most atherosclerotic lesions grow outward, but a consistent burden of atherosclerosis can exist in the absence of stenosis. In the setting of acute coronary syndrome (ACS), Rioufol et al [4] demonstrated that vulnerable plaques were

Fig. 3 The functional evaluation of stenosis confirmed that the stenosis on the left anterior descending artery was not significant with a fractional flow reserve value after intracoronary adenosine of 0.88 (normal value >0.80).

Fig. 4 The coronary angiography of patient 2 documented a tight stenosis in a very large marginal branch.

Fig. 5 The fractional flow reserve values recorded at baseline, after intracoronary administration of nitrates and after stenting were 0.67, 0.73 and 0.95, respectively. The first two values are pathological and confirmed the critical stenosis able to determine myocardial ischemia.
present throughout the coronary tree, regardless of the culprit lesion.

So the pathophysiology of ischemic heart disease seems to be heterogeneous and more complicated.

Several published series have demonstrated that a number of patients with symptoms and signs of ischemic heart disease had no stenosis at coronary angiography, both in stable and acute scenarios. In ACS, the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIb trial demonstrated that approximately 30% of patients had no culprit lesion [5]; the same result was confirmed recently by the Coronary Artery Spasm in Patients With Acute Coronary Syndrome (CASPAR) study, which also documented that epicardial coronary vasospasm was responsible for the ACS in half of the cases [6].

As for stable angina, the CASS Coronary Artery Surgery Study (CASS), involving 21,487 angiograms, showed that 18.8% of patients had nonobstructive coronary artery disease [7] and, among women, this percentage rose to 50%, as documented by the Women’s Ischemia Syndrome Evaluation (WISE) study [8].

Likoff et al [9] and Kemp et al [10] reported two studies in which patients, despite normal coronary angiography, presented with ECG changes (ST-segment depression or T wave inversion) at rest that were accentuated during exercise. Abnormalities in coronary flow and metabolic responses to stress were reported over the years by several groups, all findings consistent with a microvascular etiology for ischemia and symptoms [11,12]. So the general effort of the cardiological community must be to direct cardiac investigations to the study of ischemic heart disease beyond the search for coronary obstruction, but towards the ultimate goal of investigating a dynamic system that encompasses several pathophysiological mechanisms. Coronary atherosclerosis and vasospasm are the most common pathways, but many other contemporary mechanisms are involved.

**Conclusion**

Our cases highlight myocardial ischemia at the center of acute syndromes, representing the central sun of an ideal solar system in which many orbiting planets/players are involved. These planets/players include atherosclerosis and vasospasm (the two examples of our report), but also microvascular dysfunction, inflammation, endothelial dysfunction, platelet activation and coagulation. In daily practice, this different approach can be useful in obtaining a deeper understanding of the mechanisms underlying ischemia, offering the opportunity to tailor treatment in a specific patient or to develop strategies that can protect myocytes from ischemic damage. Such personalized medicine should be our ultimate goal.

**References**

History of coronary revascularization

Spencer B. King III, Saint Joseph’s Heart and Vascular Institute, Atlanta, Georgia, USA

Correspondence: Dr Spencer B. King III, Saint Joseph’s Heart and Vascular Institute, 5665 Peachtree Dunwoody Road, Atlanta, GA 30309, USA Tel: 678-843-5720, fax: 678-843-7339 e-mail: Spencer.King@emoryhealthcare.org

Abstract
Coronary revascularization evolved from an understanding of the relationship between coronary obstructions and the clinical manifestations they produce. Visualization of the coronary arteries in patients was necessary, and coronary arterography made that possible. Peripheral vascular surgical techniques were logically applied to the coronary circulation as technology for cardiac surgery had been developed. The concept of nonsurgical revascularization of the coronary arteries arose from the catheter-based opening of stenotic peripheral arteries. Interventional techniques including stenting are now finding their proper place alongside surgery as life-saving and life-enhancing therapies. Appropriate application of coronary revascularization in addition to modern medical therapy is now a principal focus.

Keywords: Coronary angioplasty; coronary artery bypass graft surgery; percutaneous coronary intervention; revascularization stenting

Introduction
Revascularization of coronary arteries could only be realized from an understanding of the function of coronary arteries. It is not the intention of this paper to recount the history of cardiology, but it is interesting to reflect on the fact that Galen’s flawed concepts of the circulation were promulgated from the second century until the renaissance. Had Leonardo da Vinci had enough time, this genius would probably have developed all approaches to revascularization, and perhaps he did and the drawings were lost. I think our modern experimental methods, as they relate to coronary revascularization, were understood by the man who made one of the greatest contributions to public health, Edward Jenner (1749–1823), the discoverer of the vaccine against smallpox. Jenner’s bedside observations and postmortem examinations led him to link angina pectoris with coronary obstructions. Sir James MacKinzie (1853–1925) subsequently advocated the ischemic origin of angina and its relation to coronary obstructions. Amazingly little was added or could be added to the concept that something could be done about this until technology developed that could enable investigations in living patients. Without Roentgen, nothing would have been seen. Without Forssman, Klein, Courmand and Richards, catheterization of the vascular system would not have been possible, and without Sones the chance to intervene would not have been appreciated.

Although there were other approaches to the indirect visualization of the coronary arteries, it was not until Mason Sones inadvertently injected a coronary artery in 1958 and subsequently developed direct coronary arteriography, that the many ideas of how to perform coronary revascularization could be perfected (Fig. 1) [1].

Surgical revascularization
With the availability of coronary arteriographic images, it became conceivable that coronary revascularization could be accomplished. The angiographic extent and prognostic implication of
coronary heart disease stimulated interest in doing something about it. Studies from the Cleveland Clinic showed very different outcomes of medical therapy based on the number of vessels with obstructions [2]. The Vineberg procedure of placing the bleeding internal mammary artery into a tunnel in the left ventricular myocardium and waiting for collaterals to form was soon replaced with direct revascularization using saphenous vein grafts. Leading this effort was Dr Rene Favaloro. Others had performed patch grafting of the coronary, developed by Senning [3], and a coronary artery bypass graft procedure had been performed as early as 1964 by Garrett when a complication of a coronary endarterectomy occurred [4]. However, it was Favaloro more than others who pioneered the saphenous vein bypass approach (Fig. 2). Among others who were pushing the envelope were Dudley Johnson of Milwaukee, who showed that multiple grafts to distal coronary segments could address diffuse disease, and George Green of New York, who performed direct internal mammary to coronary anastomoses. The techniques evolved rapidly with advances in anesthesia, cardiopulmonary bypass, myocardial protection and surgical equipment and supplies. By 1974, the Cleveland Clinic coronary artery bypass grafting surgery mortality rate was only 1.4%, and graft patency was 94% [5]. The stage was set for trials of the technique. The National Heart, Lung and Blood Institute funded the Coronary Artery Surgery Study (CASS) [6]. The randomized CASS enrolled 780 patients who were mildly symptomatic or had no symptoms, and although there was no overall survival benefit of revascularization, the patients with abnormal left ventricular function and three-vessel or proximal left anterior descending (LAD) artery plus circumflex disease did benefit. Other trials, such as the VA Cooperative Trial [7] and the European Coronary Surgery Study [8], studied more symptomatic patients. Based on those trials, surgical revascularization for patients with more extensive disease became the recommended treatment to improve survival. Following those trials, all started in the 1970s, information about surgical revascularization was primarily gained from registries and observational data. For significantly symptomatic patients, surgery usually eliminated angina and the technique flourished.

### Percutaneous revascularization

The idea of percutaneous revascularization grew from a confluence of the radiographic knowledge of the coronary pathoanatomy, the success of bypass surgery and the technical development of peripheral vascular revascularization pioneered by Charles Dotter of Portland, Oregon. It was the crude coaxial catheter technique developed by Dotter that inspired Andreas Gruentzig to conceive a catheter-based method of revascularizing narrowed or obstructed coronary arteries with a balloon catheter. After gaining experience with the non-compliant balloon built for peripheral vascular use, animal experiments confirmed that he could open obstructed coronary arteries with a small catheter-delivered balloon and eliminate the obstruction (Fig. 3). In September 1977, the first patient with disabling angina and a proximal left anterior descending stenosis underwent angioplasty (Fig. 4). The first successful cases were presented
at the American Heart Association’s scientific sessions later that year to an astonished audience that included Mason Sones. The rush was on to visit Gruentzig in Zurich and adopt the technique [9]. It should be pointed out that angioplasty was first applied to treat angina pectoris in patients who had suitable stenoses and otherwise would have had surgery [10]. Support for Gruentzig’s efforts in his home institution was mixed. Interestingly, the surgeon who offered support and encouragement was the same Ake Senning who had first developed the technique of endarterectomy and patch grafting to provide coronary revascularization before the emergence of vein graft surgery. Although Gruentzig was able to conduct live demonstration courses and to train the early adopters, he became frustrated with restrictions placed on him in Zurich and was convinced to join the laboratory of the present author at Emory University in Atlanta in 1980. Many pioneers expanded percutaneous coronary revascularization. John Simpson developed a catheter that could be placed over a guidewire. Subsequent steerable guidewires enabled treatment of more remote coronary lesions. One of the greatest successes of percutaneous revascularization has been the emergency reperfusion of occluded coronary arteries causing acute myocardial infarction. The work of Raymond Erbel in Germany and Geoffrey Hartzler in Kansas City was pivotal in perfecting this approach, which has been life saving and has gained worldwide acceptance.

The main drawbacks of angioplasty were the unstable lumen post procedure leading to acute occlusion, and the later restenosis that occurred in over 30% of patients. The “new device era” evolved to try to overcome these issues. Multiple devices, including atherectomy catheters and lasers were developed to remove plaque but have been largely abandoned. Only stents have remained and have become the default percutaneous therapy. Stents stabilize the artery acutely, dramatically reducing the need for emergency surgery after a failed angioplasty. Restenosis caused by excessive healing response was a continuing problem until antiproliferative drugs such as paclitaxel and rapamycin were incorporated onto the stents.

Percutaneous revascularization has been tested against surgical intervention and against medical therapy alone. From the earliest trials, such as the Emory Angioplasty Versus Surgery trial [11] and the Bypass Angioplasty Revascularization Investigation [12], it was learned that percutaneous approaches could be employed for appropriate multivessel patients without increasing the risk of death or myocardial infarction compared to bypass surgery. After major advances in stenting and surgery, the most current comparison, the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial [13], identifies patients who can safely undergo stenting and other more complex subsets that have superior outcomes with surgical revascularization. Although there is little debate about revascularization for patients with acute coronary syndromes, the use of revascularization for stable coronary disease remains controversial. The Clinical Outcomes Utilizing

---

Fig. 3 Early dog experiments by Andreas Gruentzig. Photo provided by Maria Schlumpf, Zurich.

Fig. 4 First patient to undergo successful percutaneous transluminal coronary angioplasty.
Revascularization and Aggressive Drug Evaluation (COURAGE) trial [14] and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial [15] selected patients with known coronary anatomy for revascularization or medical therapy only. A clear survival advantage for revascularization could not be shown in these patients with less than severe obstructive disease. A current trial using fractional flow reserve to document major artery flow-limiting stenoses favors revascularization [16], and an ongoing trial, ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches), will study patients without disabling symptoms who have extensive ischemia on noninvasive perfusion scanning.

A population of major interest since the BARI trial is those patients with diabetes and multivessel disease. When the trials of angioplasty and those using bare metal stents were analyzed using patient-specific data, an advantage for surgery over percutaneous intervention was found [17]. The most definitive study in patients with diabetes using drug-eluting stents, the FREEDOM (Future REvascularization Evaluation in patients with Diabetes Mellitus) trial, will report the 5-year outcome at the American Heart Association’s scientific sessions in November 2012. Aside from the remaining questions about the value of coronary revascularization for the prevention of premature death and myocardial infarction, the benefit of relieving obstruction and restoring nutritive coronary flow is the most effective therapy for angina pectoris and disabling symptoms. A more detailed review of the history of surgical and percutaneous revascularization can be found in a monologue by Drs Favaloro, Tom Ryan and the present author [5,18–20].

Conclusion

Now, 83 years from the first coronary catheterization, 54 years since the first selective coronary arteriogram, 50 years since the development of surgical coronary revascularization, and 35 years from the first percutaneous coronary revascularization, we have learned much about the effectiveness of restoring coronary blood flow. It is not surprising that the more obstruction, the more ischemia, the more symptoms – the greater the benefit of revascularization. The next frontier is to understand better how to retard the development of coronary obstructions through metabolic interventions, and how to identify and interdict the catastrophic events resulting from suddenly occluded coronary arteries.

References

In 2007, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial found that percutaneous coronary intervention (PCI) on top of optimal medical therapy (OMT) versus OMT alone, did not reduce the risk of death, myocardial infarction (MI), or other major cardiovascular events of patients with coronary artery disease (CAD) [1].

In 2009, the FAME study showed that the routine measurement of fractional flow reserve (FFR) in patients with multivessel CAD undergoing PCI with drug-eluting stents significantly reduced mortality and MI when compared with standard angiography-guided PCI [2].

The FAME-2 study published in 2012 somehow attempted to test the findings of the COURAGE and FAME studies together, and investigated the efficacy of FFR-guided PCI versus OMT in stable CAD [3]. There was a highly significant difference in the incidence rate of the primary endpoint (a composite of death from any cause, nonfatal MI, or unplanned hospitalization leading to urgent revascularization during the first 2 years) between treatment arms, which was driven by a lower incidence of urgent revascularization in the PCI group. The study was terminated prematurely and the authors concluded that an FFR-guided PCI strategy significantly improved clinical outcomes.

In that study the overall number of events was small (only 56 patients required urgent revascularization) and the definition of the need for urgent revascularization was primarily clinical in the vast majority of patients. However, a careful analysis of the data allows for completely different and seemingly contradictory conclusions.

First of all, stenting was once again shown not to save lives or prevent heart attacks, whereas the OMT strategy was confirmed to be quite effective, with more than 80% of patients presenting symptom free and only 19.2% with a Canadian Cardiovascular Society angina scale of II–IV. Bearing in mind the limitations when comparing data from different studies, the FAME-2 trial also showed that the recurrence rate of angina in patients treated with medical therapy has decreased from 42% at 1 year in the COURAGE trial to 19.2% at 6 months in the FAME-2 trial. Conversely, despite coronary revascularization, 10% of the treatment group was still symptomatic at 6 months. Of note, patients in the registry cohort, who by definition had an FFR of more than 0.80 in all vessels, had comparable angina symptoms to those in the two study groups.

What is more, the PCI group had a 104% chance of undergoing revascularization, whereas only 12.7% of patients required a similar intervention in the medically managed group. In other
words, a patient with stable angina treated with medical therapy is much less likely to require coronary intervention even when presenting with significant CAD and low FFR.

Importantly, following invasive assessment with FFR, 11 patients with significant obstructions need to be treated in order to prevent one urgent revascularization (number needed to treat = 10.53). In this way, one would unnecessarily and prematurely expose 10 patients to revascularization-related complications (i.e., stent thrombosis, restenosis, etc.), an aspect that could not be assessed in the present work because of the short follow-up. Keeping in mind that coronary revascularization would not change patient outcomes in terms of death and MI, would it not be more prudent and cost-effective to manage patients with OMT until and if "urgent revascularization" is needed?

Indeed, the FAME trial documented a lower mortality rate in patients undergoing evaluation with FFR; however, also because of a short follow-up, a similar result could not be documented in the FAME-2 study. Nonetheless, the main difference between the two trials is that FFR led to fewer PCI procedures in the earlier study [2].

However, there is some disturbing new evidence with regards to OMT as well! In clinical practice OMT is represented by an association of angiotensin-converting enzyme inhibitors, aspirin, β-blockers and lipid-lowering therapy (statins). The efficacy of angiotensin-converting enzyme inhibitors [4], aspirin [5] and statins [6] for the primary or secondary prevention of cardiovascular events has been confirmed in recently published studies; however, the rationale for using β-blockers for primary and secondary prevention has been extrapolated from the benefit obtained with these agents in patients post MI, with no data directly testing the effect of β-blockers in the primary and secondary prevention of cardiovascular disease.

A recently published observational, propensity score matching study compared outcomes with and without β-blocker therapy in about half of more than 44,000 participants in the REACH registry who had previous MI, CAD without MI, or CAD risk factors only. In both cohorts with CAD, the risk of cardiovascular death, MI, or stroke did not differ significantly between β-blocker recipients and non-recipients, whereas in the risk factor-only group, the risk was significantly higher (by 18%) in β-blocker recipients than in non-recipients. Only in patients with recent MI (1 year), were β-blockers associated with a significant reduction in the risk of major coronary events, including hospitalization for an atherothrombotic event or revascularization (odds ratio 0.77; 95% CI 0.64–0.92) [7].

Conclusions

In conclusion, how should this new evidence affect the treatment of patients with established, or risk factors for, ischemic heart disease?

Although the results of these studies unsettle some of our common beliefs and leave many open questions, what we learn is that, in stable angina, revascularization might be confidently reserved only for those patients with refractory angina after intense medical management, bearing in mind that omitting β-blockers might not affect the outcome in terms of cardiovascular events.

References