Coronary flow and physiology beyond the stenosis

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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

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Basic Article

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. As in straight blood vessels,

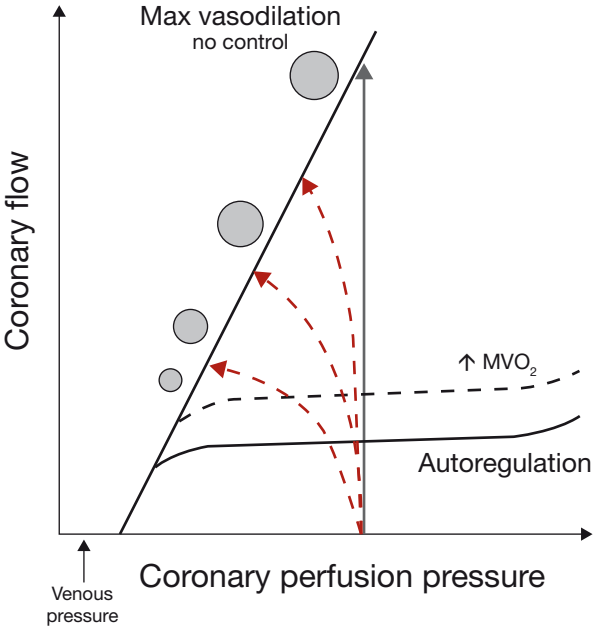

Fig. 2 *Coronary pressure–flow relationship. At rest, flow is maintained over a large range of physiological pressures by a parallel change in resistance. The dashed line indicates autoregulation at higher oxygen consumption. At maximal vasodilation, flow can increase up to about five times in the absence 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. MVO_2 = myocardial oxygen consumption.*

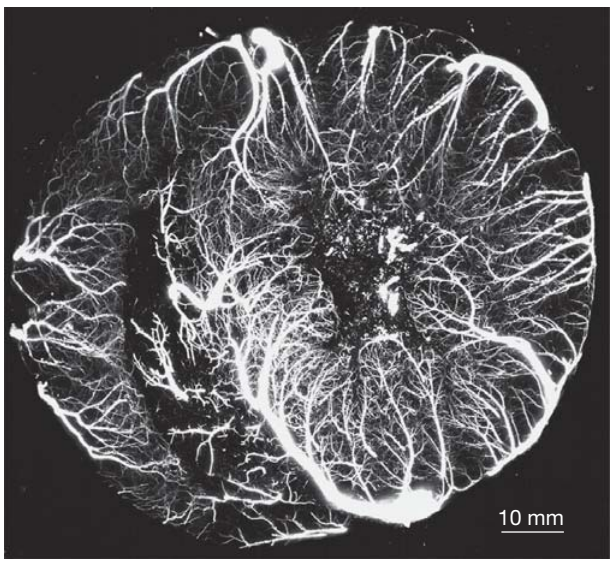

Fig. 1 *Architecture of coronary microvessels in a dog heart. These 3-dimensional data were obtained by alternately cutting and imaging (at 40 μm resolution) the frozen specimen, which was infused with fluorescent vascular casting material. Note the intricate arrangement of coronary microvessels as they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

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

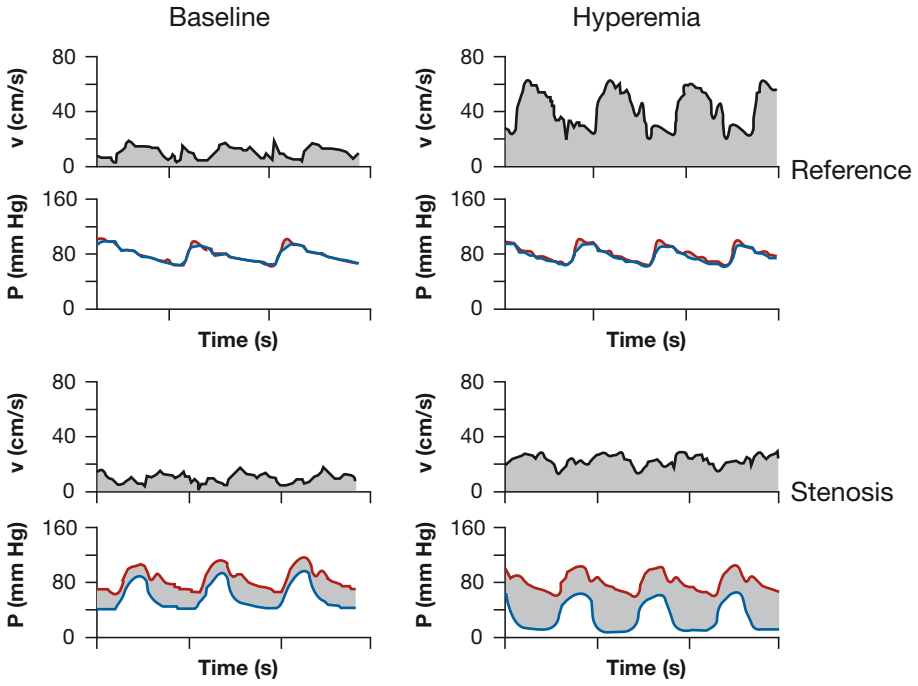

Fig. 3 *Coronary pressure and velocity waveforms measured in a patient at rest and hyperemia (right) in the absence (top) and presence (bottom) of a stenosis. At baseline, coronary flow was hardly affected by the stenosis, albeit at a higher pressure loss. During hyperemia, flow increased almost 3-fold 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.

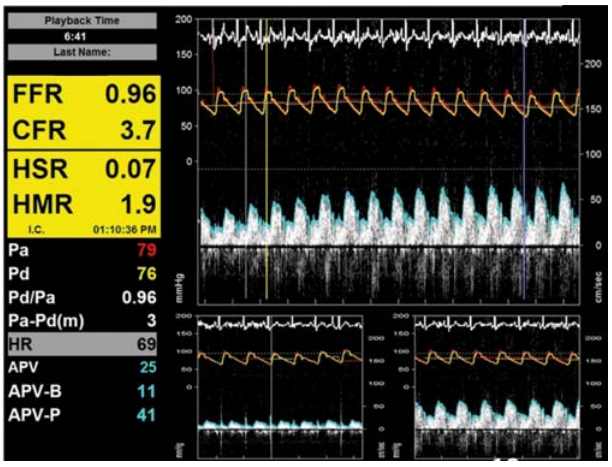

Fig. 4 Screenshot of the instrument console (Combomap®, Volcano, USA) showing the relevant pressure and velocity signals and hemodynamic indices obtained in a reference vessel of a patient. CFR = coronary flow reserve, FFR = fractional flow reserve, HMR = hyperemic microvascular resistance, HSR = hyperemic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

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. •

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