Coronary flow reserve measurements in hypertension

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Arterial hypertension can provoke a reduction in coronary flow reserve through several mechanisms that are not mutually exclusive (coronary artery disease, left ventricular hypertrophy, microvascular disease). The diagnostic management should include exploring these different targets with different diagnostic markers. In clinical practice one should keep in mind that assessing global cardiovascular risk of hypertensive patients into low, medium, high, and very high class is the primary goal. Global risk stratification follows the diagnostic routine procedures suggested by the 1999 World Health Organization-International Society of Hypertension guidelines: medical history, physical examination, and clinical blood pressure measurement; routine blood chemistry and urine analysis; and ECG [1]. In large cohort of hypertensive patients, however, Cuspidi et al [2] showed that this routine work-up may be too insensitive to detect patients belonging to high global risk category. Additional diagnostic procedures seem mandatory, such as routine cardiac [3,4] and vascular ultrasonography [2], to avoid this error [2]. This article discusses variables of coronary flow regulation as far as they seem crucial for the understanding of diagnostic procedures to assess coronary flow reserve in arterial hypertension.

The coronary circulation is unique because it perfuses the organ that generates the perfusion pressure for the entire circulation. The major determinants of coronary blood flow are aortic pressure, extravascular compression, myocardial metabolism and energy demand, structural architecture, and neurohumoral and endothelial control of coronary vascular resistance. Interfering variables that affect maximum coronary blood flow and coronary
reserve are perfusion pressure gradient along the coronary vascular tree, distribution of coronary vascular resistance, transmural gradients of coronary flow, heart rate, left ventricular mass and volume, left ventricular wall stress and end diastolic pressure, and rheologic parameters [5].

**Architecture of coronary vasculature**

The coronary arteries branch into smaller arteries that intrude from the epicardium into the myocardium to reach the subendocardium by a dichotomic-fractal order. Coronary angiography can give information about coronary lumen diameters down to vessels of 500 to 1000 μm, still representing coronary conduit arteries. Coronary arteries that take part in the control of coronary resistance have diameters in the range of 100 to 300 μm, followed by coronary arterioles (10–100 μm). The preterminal coronary arterioles go into capillaries that represent the true exchange area of oxygen and substrate for myocytes. Coronary veins drain the exhausted blood from the capillary bed. The total coronary length is estimated to be composed by 60% to 75% of coronary arterioles, whereas intramural arteries contribute 15% to 25% and epicardial coronary arteries 5% to 10% [6]. From the anatomic point of view, arterioles represent an important part of the coronary circulation that escapes the analysis of coronary angiography. The coronary resistance is represented 50% to 60% by arterioles, whereas capillaries and venules contribute about 20% and small arteries 20% to 30% [7].

**Coronary flow and coronary vascular resistance**

The effective perfusion pressure gradient for coronary inlet blood flow, predominately during diastole, is the aortic pressure minus the intramyocardial tissue pressure, and the coronary venous pressure. Only the coronary arteries supplying the right ventricle have less pronounced systolic-diastolic phase shift in coronary blood flow. Myocardial extravascular compression of the coronary circulation is related most easily to intraventricular pressure [8]. Back or venular pressure in the coronary circulation is most likely reflected by the right atrial pressure. The pressure in the aorta, in the right atrium, and in the left ventricle (alternatively the pulmonary wedge pressure) should be determined simultaneously in each patient under study for clinical assessment of coronary flow reserve. Coronary vascular resistance is defined by the ratio of mean aortic pressure minus right arterial pressure to the coronary blood flow. The ratio of coronary vascular resistance at maximal coronary vasodilation to that at baseline provides a more precise approach to describe the regulatory range of coronary vascular bed, taking into account differences in aortic pressure as the major determinant of coronary blood flow [5].

The coronary vascular resistance is critically controlled at the level of the resistive vessels (<300 μm), provided no stenosis is present in the epicardial
conduit arteries [9]. The tone of prearterioles and smaller arteries (100–300 μm in diameter) is largely controlled by flow, distending pressure, myogenic tone, autonomic nervous system, and endothelial function [10]. In the distal compartment of resistive vessels the tone of the arterioles (<100 μm) is critically dependent on myocardial metabolism. Coronary resistance co-exists in different arteriolar compartments and its distribution may change along the coronary vascular tree [9].

**Transmural gradient of coronary blood flow**

The vessels in the inner subendocardial layers of the myocardium are exposed to greater intramyocardial pressure than those in the outer layers. The gradient of intramyocardial pressure from endocardium to epicardium is the basis for a potential difference in transmural blood flow distribution. Under baseline conditions the subendocardium uses a greater fraction of its maximum coronary flow than does the subepicardium (endo:epi ratio 1.1:1.2). During maximal coronary dilatation (eg, reactive hyperemia following ischemia or infusion of adenosine) the endo:epi ratio may change with relative redistribution of blood volume from subendocardium to the subepicardium. In addition, the ratio of endo:epi maximum coronary blood flow is highly dependent on heart rate and falls to 0.4 at heart rates exceeding 200 per minute [8]. The most likely explanation for this observation is that systolic myocardial extravascular compression limits maximal coronary blood flow more in the subendocardium than in the subepicardium. Taken together, measures of total coronary vasodilator reserve do not necessarily reflect changes in transmural coronary vasodilator reserve. Interfering variables, such as changes in heart rate and the stimuli for induction of maximum coronary vasodilation (ischemia, atrial pacing, and pharmacologic approaches), have to be tightly controlled during measurement of coronary flow reserve [8].

**Pathophysiology of coronary circulation in arterial hypertension**

In arterial hypertension a reduced conductance of coronary circulation may be caused by several factors: disturbance of the coronary macrocirculation (conductance vessels); disturbance of the microcirculation (resistive vessels); and extravascular myocardial alterations [11]. The following section focuses on hypertension-associated alterations of coronary microvasculature.

**Functional alterations of coronary microcirculation**

Disturbances of coronary microcirculation may lead to profound reduction of coronary flow reserve and severe angina in hypertensive patients,
although flow-limiting stenoses of epicardial arteries are excluded [5]. In line with the concept that coronary endothelium is crucial for metabolic vasodilation in human coronary circulation [12] it has been shown that endothelial dysfunction of the coronary microvasculature is associated with exercise-induced myocardial ischemia. A reduced coronary flow reserve in hypertensive patients with and without left ventricular hypertrophy, but without flow-limiting coronary stenosis, has been demonstrated in response to dipyridamole [13], acetylcholine [14], papaverine [15], and ergonovine in combination with arterial pacing [16]. In addition, with increasing left ventricular mass the luminal concentration of noradrenaline in the coronary circulation of hypertensive patients increases [17]. Because noradrenaline directly constricts coronary smooth muscle and simultaneously stimulates release of dilatory nitric oxide from coronary endothelium, an imbalance of vasoconstriction and vasodilation signaling pathways may lead to hypertension-associated increase of tone of coronary resistive vessels with consecutive impairment of coronary flow reserve. Taken together, these findings imply that several functional signal transduction cascades of the coronary vascular wall are profoundly altered in arterial hypertension, that are involved in the reduction of coronary flow reserve, because of an elevated coronary vascular resistance either at rest or during maximal dilation.

Structural alterations of the coronary microcirculation

Hypertensive pressure overload of the left ventricle as of the coronary circulation implicates several consequences for the coronary circulation: (1) capillaries and myocytes are menaced to suffer damage, if perfusion pressure in this part of the coronary circulation is increased, by hyperperfusion and insudation of plasma proteins; (2) arterial and arteriolar vascular walls may be under increased wall stress; and (3) hypertrophy of myocytes leads to an increased distance between parallel orientated arterioles (relative rarefaction). According to Folkow et al [18] vascular wall stress is normalized by an increase in wall thickness accompanied by a reduction in lumen size. A reduced lumen size of arterioles can normalize terminal perfusion pressure in the capillaries but is associated with an impaired vasodilator capacity merely by geometric reasons. The thickening of the wall of resistance vessels can be caused by an increase in the number or diameter of the single smooth muscle cell in the media leading to an increase in the cross-sectional area of the vessel wall (hypertrophy) or by a reorganization of smooth muscle cells without increased vascular wall area (remodeling) [19,20]. Furthermore, a constriction of smooth muscle cells in a thickened arteriolar wall leads to an even more pronounced reduction of the lumen than under the condition of a normal wall:lumen ratio [21]. A relative or absolute decrease in the number of resistance vessels per myocardial volume in the presence of chronic increased coronary perfusion pressure may lead also to a normalized
terminal perfusion pressure. Otherwise, it has to be considered that a diminished number of parallel resistance vessels reduce vasodilator capacity. Quantitative stereologic investigations revealed a significant increase of the mean arteriolar wall area accompanied by an increase of perivascular fibrosis that was associated with an impaired coronary vasodilator reserve [22].

**Extravascular myocardial alterations**

At the level of the coronary resistive vessels left ventricular hypertrophy as a complication of chronic hypertension is associated with a profound impairment of the lower range of coronary autoregulation. Using tracer microspheres techniques it has been shown in the canine hypertrophic heart that this abnormality of local control of myocardial perfusion preferentially affects the subendocardium and may predispose the hypertrophied myocardium to ischemia in the setting of either coronary stenoses or systemic hypotension [23]. In hypertensive patients with left ventricular hypertrophy, coronary flow progressively and linearly declines at a gradual reduction of coronary perfusion pressure below 90 mm Hg. In contrast, in hypertensive patients without left ventricular hypertrophy and in normotensive controls the autoregulatory range is maintained over a broad range down to perfusion pressures of 60 mm Hg [24]. In hypertensive patients with left ventricular hypertrophy and shifted autoregulatory pressure-flow relationship downward fluctuations of diastolic pressure may become dangerous to the hypertrophied myocardium. Furthermore, wall stress, as a determinant of myocardial perfusion, increases in the natural course of hypertension, which leads to an impaired left ventricular function in the end stage of hypertensive heart disease. Taken together with the aforementioned finding of a reduced maximum flow in these hypertensive patients coronary flow reserve can be profoundly impaired in hypertensive heart disease.

**Diagnostic methods and assessment of coronary reserve**

In a large cohort of hypertensive patients Cuspidi et al [2] showed that the routine work-up for hypertensive individuals consisting of medical history, physical examination, routine blood and urine analysis, and ECG may be too insensitive to detect patients belonging to the high global risk category. Additional diagnostic procedures seem mandatory. In principle, noninvasive and invasive methods are available to estimate coronary flow reserve in hypertensive heart disease. The invasive approaches provide exact measurements of coronary flow reserve and are preferable for primary diagnosis of impaired microcirculation. The noninvasive procedures are more suitable for screening and follow-up studies to assess impact of therapeutic interventions.
Electrocardiographic tests

The ECG stress test can be used to screen patients with negative maximal test because of its high negative predicting value. In hypertensive patients without significant epicardial stenosis, left ventricular hypertrophy is often found with ST-segment depression during exercise and appropriate antihypertensive therapy (e.g., with angiotensin converting enzyme inhibitors) can induce regression of hypertrophy paralleled by reduction of ST-segment depression [25]. In case of positive, uninterpretable, or ambiguous ECG stress tests image stress test should be warranted. After the exclusion of stenoses in epicardial coronary arteries, ECG abnormalities with ST-segment depression are interpreted as the result of microvascular disturbances. This is supported by the observation that hypertensive patients exhibiting episodes of ST depression during ambulatory monitoring had significantly impaired coronary flow reserve when compared with both normotensive subjects and hypertensive patients without episodes of ST depression [26]. Left ventricular mass was not the important determinant of coronary flow reserve, a finding consistent with a previous report [16]. ECG investigations give some hints on hypertensive perfusion abnormalities and can be regarded as a monitoring and screening method.

Myocardial scintigraphy

Abnormal thallium 201 scintigraphic findings were reported in hypertensive patients without coronary artery disease but with an impaired coronary reserve of $2.2 \pm 0.8$ [27] and $2.71 \pm 0.96$ [28] as compared with hypertensive patients without reversible defects who had a coronary reserve of $3.5 \pm 1.2$ and $3.7 \pm 0.8$. Nevertheless, quantitative data cannot be derived from these methods and from pharmacologic and radiotracer characteristics, like cellular uptake (thallium 201, K⁺ analogon), long half-life, high radiation dose, limit this approach for the evaluation of coronary microcirculation. Thus a global reduction of coronary vasodilator capacity is difficult to quantify by a scintigraphic approach. Furthermore, homogeneously reduced coronary vasodilator capacity might be difficult to be disclosed because of missing normal reference volume. Perfusion scintigraphy has a high accuracy in unselected hypertensive patients, but becomes low in hypertensive patients with exercise-induced ST-segment depression [29]. Because of its low specificity in these cases, myocardial perfusion scintigraphy should be replaced by stress echocardiography [30].

Echocardiography

Contrast echocardiography combined with intracoronary or intra-aortic root injection of ultrasound contrast medium that passes through capillaries has been used to identify a region of defected myocardial contrast.
The qualitative discrimination of perfusion defects has to be differentiated from the evaluation of quantitative perfusion analysis, which is still problematic for clinical use because of different scanning conditions, poor transthoracic ultrasound window, and insufficient enhancement of the myocardial intensity [31].

Transesophageal Doppler echocardiography can image the proximal segments of the left coronary artery. With a pulsed-wave Doppler sample volume, positioned on the diastolic flow of the left anterior descending coronary artery, coronary flow can be derived from flow velocity and internal coronary artery diameter [32]. Flow velocity was measured before and after intravenous administration of dipyridamole in hypertensive patients and was found to be impaired as compared with controls. Furthermore, calculated coronary resistance was increased [33]. This method is not expensive, relatively easy to repeat in ambulatory patients, and less risky than cardiac catheterization. It has to be taken into consideration that approximately 20% to 30% of the patients cannot be investigated by Doppler because of respiration, acute changes in cardiac volume, or inadequately stable position of the Doppler signal, giving lower velocities than the true value because of the angle between the ultrasound beam and vessel direction. Perfusion scintigraphy has a high accuracy in unselected hypertensive patients, but becomes low in hypertensive patients with exercise-induced ST-segment depression [29]. Because of its low specificity in these cases, myocardial perfusion scintigraphy should be replaced by stress echocardiography [30].

Positron emission tomography

The positron emission tomography provides a noninvasive technique for regional myocardial flow measurement. Positron emission tomography allows quantitative flow measurements in segments containing less than 10 g of myocardium. Furthermore, myocardial metabolism can be evaluated, which gives the opportunity to match between myocardial flow and metabolism [34]. Tracers have been used, such as rubidium 82, gallium 68, carbon 11, ammonia N 13, or water O 15, to measure perfusion on a single passage, not influencing myocardial metabolism [35]. Regional coronary resistance may also be calculated from mean arterial blood pressure and coronary blood flow. The detection of viable myocardium is possible with fluorodeoxyglucose F 18, allowing comparing myocardial blood flow and metabolism. The short half-life of tracers is the basis for acute pharmacologic interventions to evaluate coronary reserve. Impaired coronary reserve has been found in several studies in hypertensive heart disease [34,36]. Reproducibility is high, with little intraobserver and interobserver variability. This makes positron emission tomography interesting for the follow-up of therapeutic interventions. Positron emission tomography has been shown to be useful for long-term follow-up of antihypertensive therapy [37].
Nevertheless, the method is limited by the high technical and methodologic expenditure. It has to be taken into account that transmural coronary blood flow distribution cannot be evaluated because of limited spatial resolution and regional motion abnormalities of the heart.

**MRI**

MRI has proved useful for images with excellent spatial resolution and without ionizing radiation. Combined anatomic and functional evaluation of the heart, including the evaluation of myocardial perfusion, is a promising aspect of this method, especially for serial investigations. Gadolinium chelates, which rapidly diffuse out of vascular space, are used to distinguish between normal and pathologically perfused myocardium [38]. Development of new blood pool contrast agents and the improvement of hardware and pulse sequences may give results for a clinically useful diagnostic acceptance of MRI. With respect to the significance of coronary insufficiency (with absent atherosclerosis) in patients with arterial hypertension (HT) it will be exciting to follow the progress in noninvasive approaches to detect coronary flow reserve and microvascular dysfunction (positron emission tomography, MRI, transthoracic Doppler indices) [39,40].

**Coronary sinus catheterization**

Thermodilution in the coronary sinus, invented by Ganz et al [41], is an inexpensive, widely available technique for the measurement of coronary flow requiring only right heart catheterization. Coronary sinus blood flow is mainly provided by the left ventricular myocardial blood flow, although considerable variations in anatomy may occur [42,43]. The thermodilution method does not define the mass of myocardium being drained. This may become a relevant issue when comparing flow reserve in hypertensive patients with and without left ventricular hypertrophy because absolute values for autoregulated flow in coronary sinus rise with increasing left ventricular mass. In human coronary circulation the coronary flow reserve measured with the thermodilution method is consistently and substantially smaller than Doppler-derived measurements [44]. Furthermore, the reasonable time solution of coronary flow measurement is accompanied by failing spatial resolution.

Coronary venous oxymetry, based on the Fick principle, is an indirect method that gives a continuous measurement of coronary blood flow. As coronary flow increases at maximum vasodilation the oxygen saturation in the coronary sinus increases. Some severe limitations of this method, however, have to be addressed. Right atrial reflux into the coronary sinus may affect measurement [45]. Coronary sinus oxygen saturation at baseline is not related to autoregulated coronary blood flow [46]. In addition, with
increasing oxygen saturation at baseline the relative increase in oxygen saturation at maximum vasodilation is impaired and systematically underestimates coronary flow reserve [46].

In contrast, the gas chromatographic argon method allows exact measurement of coronary blood flow at baseline and during maximum vasodilation [11,47]. The principle of this gas clearance method is the gas chromatographic determination of argon in blood samples taken simultaneously from the coronary sinus and the aorta while the patient is breathing a mixture of oxygen (21%) and the inert gas argon (79%) for at least 5 minutes [48]. According to the formula of Kety flow data are given in mL/min/100g, which allows direct comparison of hypertensive patients with different degree of left ventricular hypertrophy. The equipment required is simple and inexpensive and the method is safe. The spatial solution of blood flow measurement in the left ventricle is marginal and the time solution of measurement is limited, however, because a period for desaturation of administered argon gas has to be considered for each single intervention, so that only a few measurements can be performed within a single cardiac catheterization. This method is most suitable for patients in whom significant coronary stenosis has been excluded, to diagnose coronary microangiopathy and to dissect the impact of an altered resting and maximum coronary flow on reduced coronary flow reserve. In addition, the good reproducibility of this method with a low variation coefficient offers the possibility to assess the impact of therapeutic interventions (eg, antihypertensive long-term treatment in patients with arterial hypertension) on coronary flow reserve, provided possible differences in heart rate and blood pressure are controlled during follow-up catheterization. The clinical indication for the argon gas method refers to patients with hypertensive coronary microangiopathy, the detection of vascular involvement in patients with myocarditis, dilative and hypertrophic cardiomyopathy, and the evaluation of coronary microcirculation in the clinical course of long-term treatment of these diseases.

Angiographic methods

Angiographic methods for estimating myocardial perfusion have been reviewed recently [49]. In general these methods are based either on videodensitometry or quantification of the mean transit time for a bolus of contrast medium injected into coronary arteries. Because of the rapid development of computer software and hardware several suppliers offer packages for on-line analysis of myocardial perfusion reserve in catheterization laboratories, based on algorithms for videodensitometry evaluated recently [50]. The principle of this approach is to compare two digital subtraction angiographic images in a myocardial region of interest, obtained at baseline and during maximal vasodilation. As a prerequisite contrast medium must be injected automatically with a high pressure pump to keep
volume and rate of injection reproducible and start of injection should be
gated electrocardiographically to avoid heart cycle-dependent variations in
coronary blood flow. Several problems with videodensitometric methods
have to be addressed: (1) the possibility that contrast medium might affect
coronary vasomotion and measurement of myocardial perfusion reserve; (2)
the mistake because (blood) volume replacement during injection of contrast
medium might differ at baseline and during maximum vasodilation given
a constant injection rate; (3) to allow precise subtraction of digital frames
the patient has to hold their breath at exactly the same position during
injection of contrast medium; (4) substantial overlap of distinct myocardial
regions with different systolic and diastolic regional function (normokinetic,
hypokinetic, dyskinetic) may hamper exact analysis of regional myocardial
perfusion reserve; (5) data can be given only as a relative ratio of resting to
hyperemic myocardial perfusion. This approach, however, allows easy and
simultaneous analysis of vasomotion in epicardial arteries and resistive
vessels during routine coronary angiography. Taking into consideration the
aforementioned obstacles these angiographic methods should be restricted
to patients with preserved left ventricular function, without coronary
stenosis, or only in those patients with coronary artery disease with a single-
vessel disease, and not multivessel disease.

An alternative angiographic approach to estimate myocardial perfusion
is the measurement of mean transit times of a given bolus of contrast
medium [51]. Very recently, a fairly easy to handle approach was invented
by the TIMI 4 Study Group [52] aimed to be applicable in each
catheterization laboratory: the TIMI frame count as quantitative measure
of assessing coronary flow. The principle of the TIMI frame-counting
method is to count off-line the cineframes required for a manually injected
bolus of contrast medium to first reach standardized landmarks in the
coronary artery at a given frame rate of angiograms during routine coro-
nary angiography. Comparison with Doppler-guided assessment of coro-
nary flow in patients with coronary artery disease [46,52] and with argon
gas chromatographic method in hypertensive patients with coronary
microangiopathy revealed that the frame count method yields reasonable
estimates of coronary flow at low values (eg, for baseline flow) but by
far underestimates maximum coronary blood flow with an unacceptable
variation.

Guidewire-based methods

Intracoronary flow velocity can be measured with a steerable angioplasty
guidewire with a piezoelectric ultrasound transducer integrated into the tip
and coupled to a real-time spectrum analyzer [53]. Coronary flow reserve is
computed as the ratio of the Doppler signal at maximum to baseline
coronary blood flow velocity. More recent developments integrated the
ultrasound transducer into a Judkins-style angiographic catheter to avoid
the intracoronary use of guidewires [53]. The variation of coronary vasodilator reserve among the coronary branch arteries is less than 10%. The spatial and regional solution of Doppler measurement is excellent and allows assessing rapid changes in phasic and mean coronary flow. Doppler measurement of coronary flow reserve has been validated extensively in experimental studies [54], and in patients in comparison with exercise testing [55], positron emission tomography [56], and thallium scintigraphy [57]. In combination with either intravascular ultrasound or coronary angiography Doppler measurement allows one to calculate volumetric coronary flow with reasonable validity, and additionally this approach allows one simultaneously to assess coronary vasomotor function at the level of coronary conduit and resistive arteries [58]. Accuracy of volumetric flow measurement may be hampered by variation of the tip of the flow wire within the bloodstream. An impaired hyperemic flow velocity reserve less than 2 corresponded to reversible myocardial ischemia with high sensitivity and specificity (86% to 100%) [59]. A major limitation of this technique is instrumentation of the coronary artery with an angioplasty guidewire, which requires considerable operator experience. In more than 45,000 worldwide applications, however, less than 20 cases of complication have been reported in association with sensor-tipped guidewires [59].

Alternative techniques

Apart from routine cardiac [3,4] and vascular ultrasonography [2] risk stratification may also be complemented by measurement of microalbuminuria with redefined thresholds [60,61] and peripheral artery endothelial function, recently shown to reflect the severity of disturbed circadian patterns of blood pressure [62]. The implementation of routine measurements [63] of carotid intima-media-thickness [2], peripheral vascular compliance, and endothelial dysfunction, however, depends on more reliable and effective methods making the accuracy and reproducibility more applicable for clinical routine [64].

Summary

Taken together, the diagnostic algorithm is leaded by a simple ECG stress test. In case of ST-segment depression the preferred image test should be stress ECG to bring patients at high risk for significant epicardial coronary artery stenosis to coronary angiography (and revascularization). In case of the lack of wall motion abnormalities (during stress-echo test) or absence of epicardial stenosis one may further assess coronary flow reserve with noninvasive Doppler harmonic echocardiography. For ultimate quantitative assessment invasive procedures, such as argon dilution or intracoronary Doppler techniques, represent the appropriate approach [65].
Treatment of microvascular disease may be followed-up by these new noninvasive diagnostic approaches in future and also, at present, by monitoring ST-segment depression.

References


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