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JACC REVIEW TOPIC OF THE WEEK

Autoregulation of Coronary Blood Supply in Response to Demand

JACC Review Topic of the Week

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ABSTRACT

Although our coronary circulation evolved to meet demands during marked physical exertion for "fight or flight" survival, complex and multilayered control mechanisms reduce flow during other periods. Understanding homeostasis of resting flow provides essential insights into clinical pathophysiology. Several homeostatic mechanisms (myogenic, metabolic, endothelial, and neural) maintain sufficient baseline flow regardless of driving pressure (in aggregate, "autoregulation"). As a result, ventricular dysfunction does not arise until coronary perfusion pressure decreases to ~40 mm Hg. Straightforward clinical parameters explain approximately one-half of observed absolute resting perfusion but with wide imprecision. Resting perfusion does not associate with clinical outcomes and remains unaffected by revascularization, recovery after myocardial infarction, and treating severe aortic stenosis, thereby supporting the notion that the heart was designed for peak performance. (J Am Coll Cardiol 2021;77:2335–45) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Our coronary circulation has evolved to supply high coronary blood flow to meet the demands of marked physical exertion for "fight or flight" survival. Because such demands occur only occasionally, we have developed complex, multilayered control mechanisms that reduce coronary blood flow during other periods. Analogous to studying the governor on an engine, reviewing homeostasis of resting coronary flow provides essential insights into clinical pathophysiology.

This paper begins by reviewing the array of mechanisms used by the coronary circulation to match coronary supply to myocardial need under baseline conditions, in aggregate often called "autoregulation." Empirical data from animal and humans are then provided showing their effects. Next, the clinical factors that predict resting perfusion and its prognostic value are examined. Finally, we review the failure of device therapy to change resting perfusion, consistent with its primary goal in stable patients of improving exertional symptoms.

We do not focus on control of coronary blood flow in response to exercise or pharmacological stress, as reviewed in detail elsewhere (1). Also, we do not delve into the adaptive (2) and adverse consequences when autoregulation fails, as in situations of ischemia or infarction. Rather, our focus remains on the range of conditions under which the heart can keep its internal blood flow regulated despite perturbations or pathology. As applied physiologists, we remain astonished at the well-documented tolerance of the heart to very low coronary pressure without adverse

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ABBREVIATIONS AND ACRONYMS

BSA = body surface area

EF = ejection fraction

LV = left ventricular

PCI = percutaneous coronary intervention

PET = positron emission tomography

PRP = pressure rate product

TAVR = transcatheter aortic valve replacement

clinical events or impaired function. As clinicians, we explore what consequences autoregulation has for the use of resting measurements of coronary pressure, flow, and resistance for diagnosis and treatment.

DEFINITION OF AUTOREGULATION

Under conditions of constant metabolic need, autoregulation currently refers to the ability of the myocardium to maintain stable blood flow despite variations in coronary pressure (1). Consequently, experiments studying autoregulation must separate out multiple, interacting, cumulative, and nonlinear mechanisms by altering one variable but keeping all others constant. Ensuring stable metabolic requirements poses a large challenge because many conditions that affect coronary pressure (e.g., systemic aortic pressure) also alter myocardial oxygen consumption. In addition, narrow experimental results may carry less applicability to daily life as usually several factors change at once. For example, standing up from a chair (not "exercise," yet a perturbation) causes transient and simultaneous changes in blood pressure and heart rate, requiring numerous feedback loops for stabilization.

Before considering specific mechanisms of autoregulation, it is useful to understand their net effect, shown in **Figure 1**. Starting from the baseline condition of 110 mm Hg perfusion pressure and 60 ml/min coronary flow, sudden and sustained changes in perfusion pressure were made (3). Reductions in coronary pressure below 110 mm Hg caused a transient decrease in coronary flow, and vice versa for increases above 110 mm Hg. However, flow returned to almost the same level a short time later if the pressure remained between ~40 mm Hg and 130 mm Hg.

In contrast to the nearly linear relationship between coronary flow and pressure during conditions of exercise or pharmacological vasodilation (1), autoregulation maintains an almost constant flow over the clinically relevant range of perfusion pressures, also called the "autoregulatory plateau." An immediate implication is that "resting resistance" does not provide a unique value because the same flow exists for a wide range of pressures.

MECHANISMS OF AUTOREGULATION

How does the body achieve this autoregulation that maintains constant resting flow over a wide range of perfusion pressures? As visually summarized in the **Central Illustration**, 4 categories of mechanisms provide likely redundant levels of control, although most of the data come from animal models with uncertain translation to humans. First, "myogenic" control adjusts vessel diameter inversely to vascular smooth muscle stretch. Increased stretch prompts relative vasoconstriction, whereas decreased stretch triggers intrinsic coronary artery smooth muscle relaxation. In some older literature (4), this myogenic mechanism was synonymous with the term "autoregulation" that has since grown in scope to encompass additional pathways.

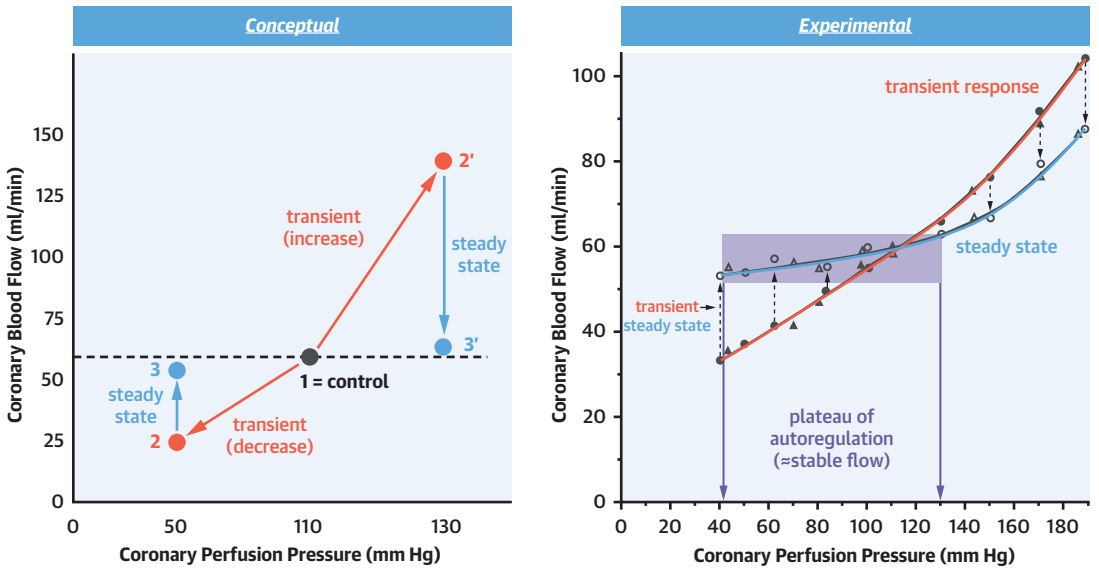
Second, "metabolic" control refers to vasodilation in association with accumulating molecules such as carbon dioxide (and hence pH) and adenosine. Although conceptually attractive given their obvious relationship to metabolic activity, it has been difficult to show a consistent change between venous oxygen content from the coronary sinus and either blockade of the receptors for these molecules (e.g., using aminophylline for adenosine) or degradation of the molecule itself (e.g., using adenosine deaminase [5]). Variation among species adds heterogeneity, as adenosine seems to contribute to basal regulation of coronary blood flow in swine but not in dogs (6). In addition, although adenosine triphosphate infusion produces vasodilation, and its coronary venous concentration relates linearly to blood flow during exercise and hence currently remains the dominant explanation for metabolic control (7), adenosine receptor blockade and inhibiting its downstream messenger nitric oxide did not reduce exercise-induced vasodilation in 2 different species (1). Therefore, the exact contribution of metabolic messengers to autoregulation in humans awaits further clarification.

Third, "endothelial" control includes a variety of vasoactive factors produced by the endothelium. Both nitric oxide and prostacyclin are key vasodilators, while endothelin remains the dominant vasoconstrictor. The balance between vasodilation and

HIGHLIGHTS

- Several mechanisms are responsible for the maintenance of myocardial flow at rest independent of driving pressure.
- Resting perfusion is unaffected by revascularization or aortic stenosis and is not related to clinical outcomes.
- Measurements of coronary flow and resistance at rest are less pertinent to diagnosis and treatment than those made at higher intensities of myocardial performance.

FIGURE 1 **Autoregulation**



If metabolic needs remain constant, then multiple control mechanisms produce a relatively stable coronary flow across a wide range of perfusion pressures. As conceptually depicted on the **left-hand side**, consider a coronary artery with a baseline perfusion pressure of 110 mm Hg and flow of 60 ml/min (point 1). If coronary pressure suddenly decreases to 50 mm Hg, then the flow will transiently decrease (point 2) but a short time later return to approximately the baseline flow (point 3). Conversely, if coronary pressure suddenly increases to 130 mm Hg, then the flow will transiently increase (point 2') but a short time later return to approximately the baseline flow (point 3'). As experimentally shown on the **right-hand side**, while transient perturbations produce a direct relationship between perfusion pressure and flow, the steady-state value remains remarkably fixed (**triangular points** obtained after blockade of cardiac prostaglandin synthesis with indomethacin). Reprinted with permission from Rubio and Berne (3).

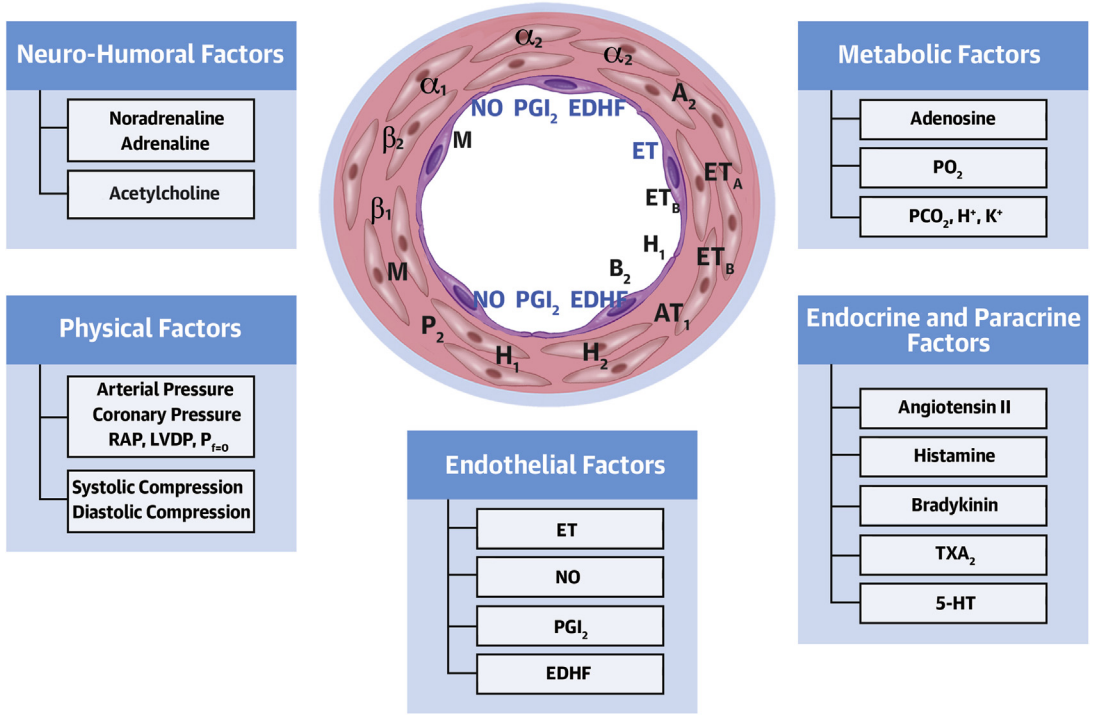
vasoconstriction depends on 3 inputs: mechanical forces (mainly shear stress), local oxygen concentration, and neurohormonal mediators (acetylcholine, angiotensin, bradykinin, and norepinephrine). In healthy endothelium, this balance tilts toward vasodilation. Pathology (atherosclerosis and risk factors) can disrupt this balance toward vasoconstriction, heterogeneously and differentially affecting endothelial function of the epicardial arteries versus coronary arterioles. Endothelial dysfunction may limit the increased coronary flow response to myocardial oxygen demands, cause diffuse or focal coronary artery spasm, or induce microvascular (arteriolar) dysfunction with or without angina.

Fourth, "neural" control encompasses both parasympathetic and sympathetic aspects. Under baseline conditions, however, autonomic control seems negligible because surgical denervation does not change resting oxygen consumption in animal models (6). Alpha and beta sympathetic nerves to the heart modify coronary blood flow by direct effects on vasomotion and indirect effects on systemic blood pressure or heart rate that alter workload and thus oxygen demands. Alpha stimulation increases blood pressure and heart rate with increased coronary flow modified by alpha-mediated direct coronary vasoconstriction, and the opposite opposing effects for alpha blockade. Beta stimulation causes direct coronary vasodilation and increased contractility that indirectly also increases coronary flow. Beta blockade lowers coronary blood flow by the opposite mechanisms, both direct and indirect. The direct neural effect of vagal stimulation is coronary vasodilation and increased coronary flow, whereas the indirect effect of lowering blood pressure and heart rate reduces myocardial oxygen demand with a net reduction in coronary flow. Vagal blockade, as with atropine, increases heart rate and blood pressure with increased oxygen demands and coronary flow that is modified by direct coronary vasoconstriction.

EMPIRICAL SUPPORT FOR AUTOREGULATION

In animal models, coronary pressure can fall dramatically; if subendocardial flow remains normal,

CENTRAL ILLUSTRATION Control Mechanisms



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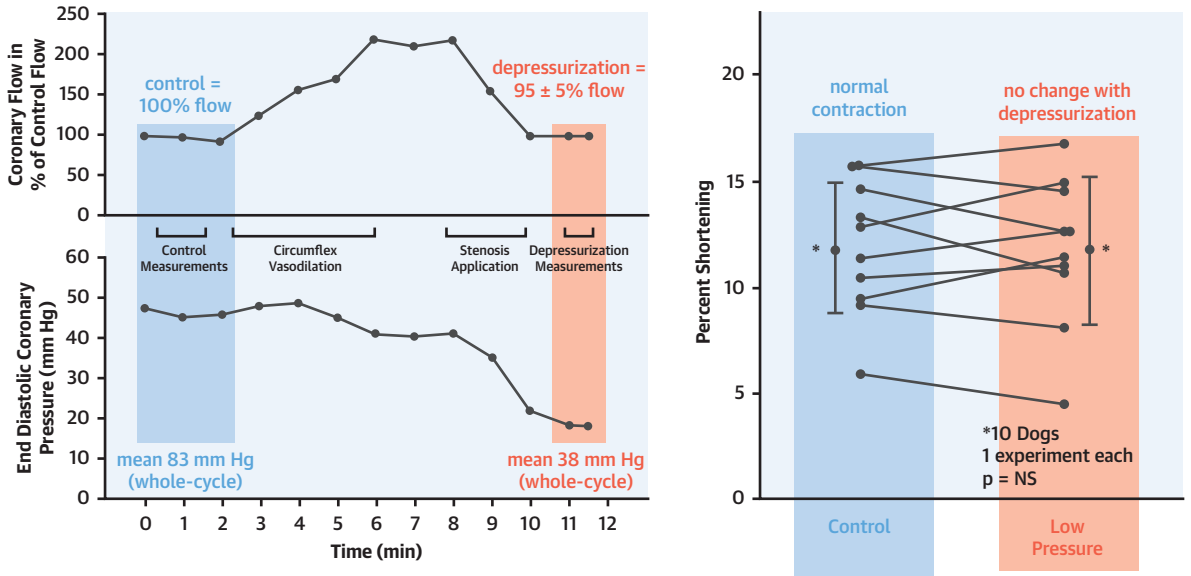
Four categories of mechanisms provide interacting, cumulative, redundant, and nonlinear levels of control: myogenic (not depicted but counteracts changes in smooth muscle stretch), metabolic (products such as partial pressure of carbon dioxide and adenosine), endothelial (mediated by factors such as nitric oxide, prostacyclin, and endothelin), and neural (alpha and beta receptors). Adapted from Duncker and Merkus (24). EDHF = endothelium-derived hyperpolarizing factor; ET = endothelin; LVedp = left ventricular end-diastolic pressure; NO = nitric oxide; PCO_2 = partial pressure of carbon dioxide; $P_{f=0}$ = zero-flow or coronary wedge pressure; PGI_2 = prostacyclin; RAP = right atrial pressure.

however, contractile function will then be preserved. **Figure 2** summarizes the results from 10 chronically instrumented dogs studied when awake and unsedated (8). Using a dipyridamole infusion and coronary constrictor, epicardial flow remained intact while coronary perfusion pressure decreased dramatically from 83 mm Hg to 38 mm Hg, corresponding to unitless coronary/aortic ratios of 83/92 = 0.90 and 38/83 = 0.43, respectively. Although transmural perfusion by radiolabeled microspheres increased by ~40% from 1.02 to 1.41 ml/min/g (due to augmented collateral flow and/or changes in perfusable tissue fraction), subendocardial perfusion remained intact at 1.11 ml/min/g before depressurization and 1.21 afterward, as did percent myocardial shortening. Therefore, a decrease in mean coronary pressure to near 40 mm Hg did not affect baseline percent shortening given the preserved subendocardial blood flow.

Figure 3 summarizes myocardial thickening as a function of coronary pressure distal to a variable stenosis in 16 chronically instrumented dogs studied with light intravenous sedation to stabilize hemodynamics (9). Over a wide range in mean coronary pressure from 100 mm Hg to ~40 mm Hg (essentially corresponding to the range of autoregulation described earlier in **Figure 1**), contractile function remained normal. Although somewhat variable among the 16 animals, a linear decrease in systolic performance began around 40 mm Hg and ceased at 20 mm Hg.

This lower bound of autoregulation near 40 mm Hg has received further support from human studies (10). As part of the first clinical validation of fractional flow reserve, a series of patients with intact left ventricular (LV) function underwent same-day assessment of myocardial perfusion (using positron emission tomography [PET]) and invasive coronary pressure

FIGURE 2 **Depressurization But Intact Flow**



In 10 chronically instrumented dogs, percent shortening did not differ between control conditions (mean coronary pressure 83 mm Hg with transmural microsphere perfusion 1.02 ml/min/g) and depressurized conditions (mean coronary pressure 38 mm Hg with transmural microsphere perfusion 1.41 ml/min/g). Reproduced with permission from Smalling et al. (8).

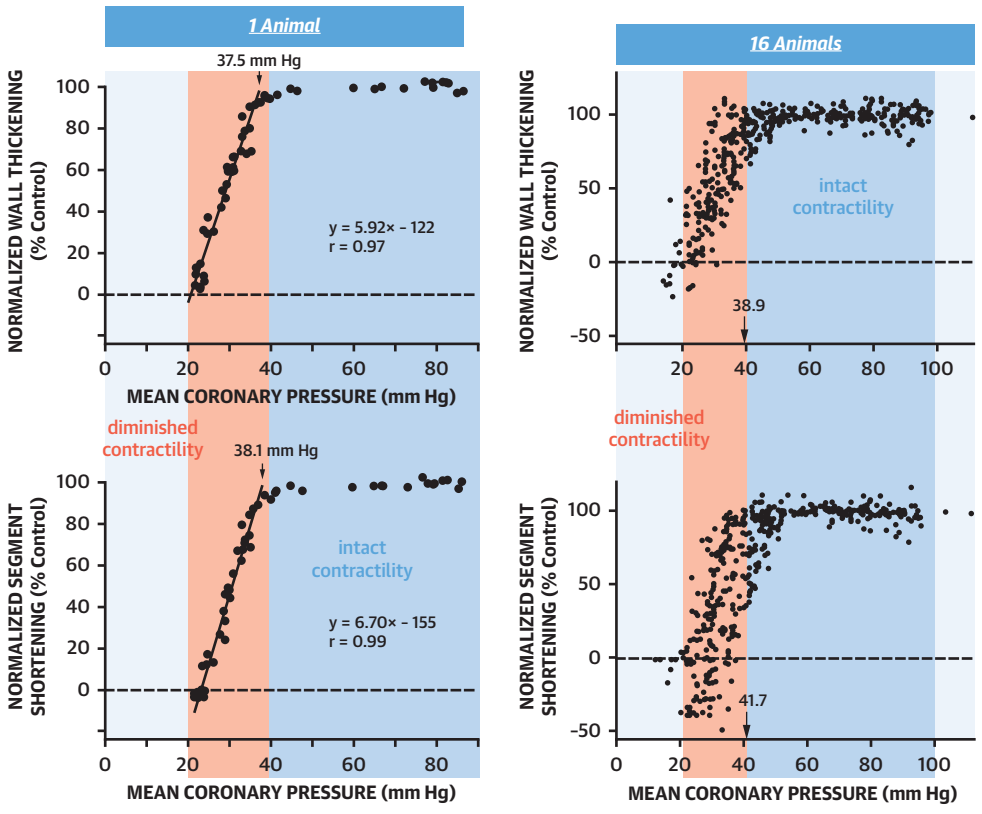
assessment distal to a stenosis. **Figure 4** presents the near constant baseline perfusion over a wide range of coronary pressures, with the lowest observation at ~45 mm Hg.

Together, the aforementioned observations in awake animals (8,9) and humans (10) indicate that myocardial perfusion remains stable via autoregulation to satisfy contractile need down to a coronary perfusion pressure of ~40 mm Hg. Between ~40 mm Hg and 20 mm Hg, wall thickening or segment shortening decreases from normal to akinesis (9). Below a coronary pressure of ~20 mm Hg, a variable assortment of dysfunction, necrosis, stunning (repetitive episodes of stress-induced ischemia that reduce baseline contractile function despite normal perfusion and pressure between ischemic episodes) (11), or hibernation (reversible contractile dysfunction without necrosis due to metabolic adaptation from chronically reduced flow) (12) occurs depending on acuity, duration, repetition, collateral supply, and biologic heterogeneity.

As a somewhat teleologic explanation for why the regulation of resting perfusion is so complex, multilayered, and refined, the animal studies (9,13) summarized in **Figure 5** should be considered. Both studies show that almost any reduction in resting flow produced an impairment in myocardial performance. Therefore, the myocardium has essentially no tolerance for reduced resting flow. A clinical consequence of this tight coupling between resting flow and contractile function arises during primary percutaneous coronary intervention (PCI): no acute benefit can be expected from stenting a nonculprit lesion that supplies a normally contracting segment (although long-term benefits exist, as for PCI outside of an acute infarct). Stated another way, normal ventricular function indicates intact resting flow regardless of epicardial coronary severity.

Further understanding of the clinical relevance of autoregulation requires analysis of quantitative resting perfusion in a large human cohort to assess multiple interacting mechanisms. Consequently, we studied our previously reported database of patients and research subjects undergoing absolute flow quantification using cardiac PET (14). A total of 3,922 scans had a baseline ejection fraction (EF) assessment and no significant resting defect (<5% of the left ventricle with relative uptake <60% of maximum). Overall a very weak correlation existed between baseline EF and absolute perfusion in ml/min/g averaged over the entire left ventricle (Pearson $r = 0.172$; $p < 0.001$), indicating that a small minority ($0.172^2 = 2.9\%$) of the variation between these 2 parameters could be explained before multivariable

FIGURE 3 Ventricular Performance With Decreasing Pressure



In 16 chronically instrumented dogs, wall thickening or segment shortening remained intact with progressive coronary constriction until the coronary pressure reached ~40 mm Hg, then decreased in linear fashion until reaching akinesis about 20 mm Hg, although variation existed in these thresholds among animals. Reproduced with permission from Canty (9).

adjustment that would further weaken their independent relationship. Among outliers of resting perfusion (top and bottom 1%, corresponding to thresholds of 0.50 and 2.00 ml/min/g, respectively), observed EF ranged from <30% to >70% at each extreme, indicating that very low and very high resting perfusion cannot predict EF in an individual subject.

FACTORS AFFECTING RESTING PERFUSION

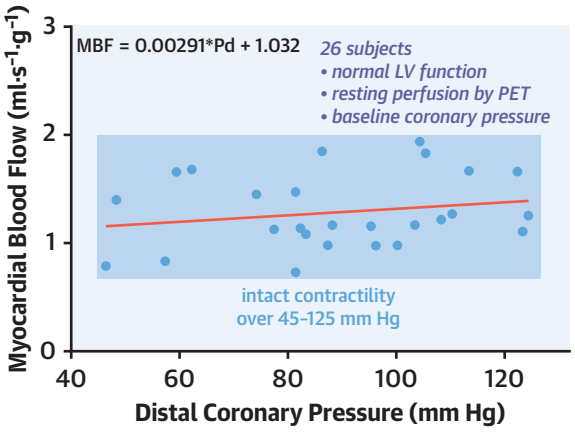
Myocardial oxygen requirements can be conceptually divided into 5 components (15). First, even an artificially arrested heart has basal metabolic needs to maintain cellular structure and viability. Second, electrical conduction and repolarization use some amount of energy. The remaining 3 categories correspond to mechanical phases of the cardiac cycle: isovolumetric contraction, systolic ejection, and diastolic relaxation. Together, these 5 aspects account for >90% of the observed variation in myocardial oxygen consumption over a wide range of experimental conditions in an animal model (15). Because just 10% to 20% of total oxygen consumption services basal metabolism and the electrical system (1), mechanical work accounts for the vast majority.

Stated another way, myocardial oxygen requirements depend mainly on contractility, heart rate, and wall stress (both preload and afterload). For some of these factors, the applicability to humans has been limited by a lack of straightforward clinical parameters. A study of >20 proposed formulae (15) found that some of the strongest predictors required assessment of dP/dt_{max} (peak rate of change in LV pressure, corresponding to contractility) or stroke volume, hence difficult in routine practice. However, formulae focusing on the product of pressure and heart rate have shown reasonably robust correlations with myocardial oxygen consumption and thus have been widely applied.

To quantify clinical factors associated with resting perfusion, we studied our previously reported database of patients and research subjects undergoing absolute flow quantification using cardiac PET (14). Of the >80 clinical variables collected, the vast majority (~75%) showed a significant univariate association with baseline perfusion in ml/min/g averaged over the entire left ventricle. When combined into a multivariable model, the strongest predictor remained the pressure rate product (PRP), computed as systolic blood pressure multiplied by the heart rate at rest. As shown in **Figure 6**, baseline PRP related directly to resting perfusion as expected by combining 2 major factors affecting myocardial oxygen requirements: heart rate and afterload. However, the correlation was modest at ~0.6 and indicates that only 35% of the variation could be explained. For every 1,000 mm Hg/min increase in PRP, perfusion increased by 0.08 ml/min/g.

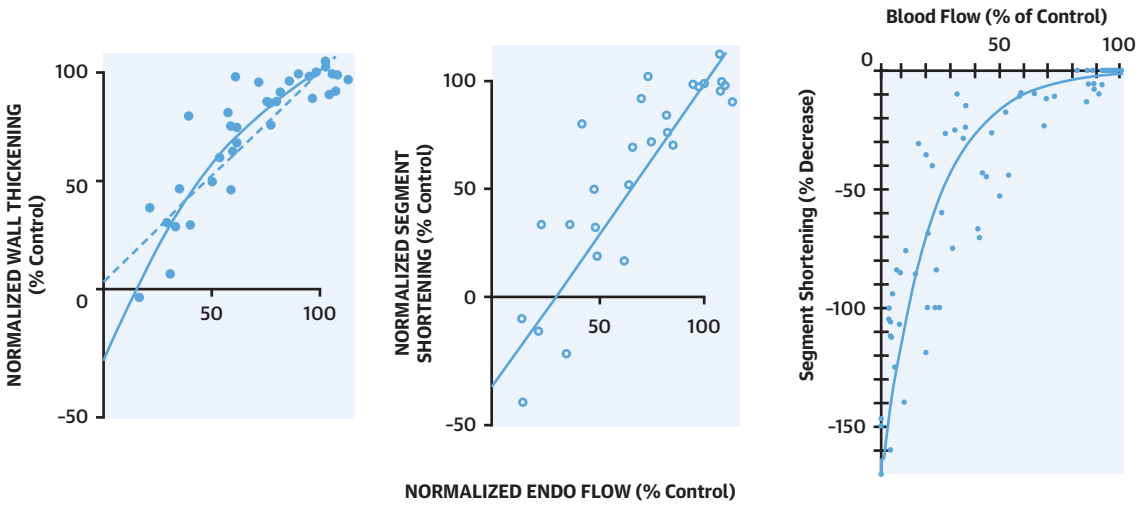
After PRP, the next strongest predictor was body surface area (BSA), computed via the Mosteller formula. Baseline perfusion displayed an inverse association such that for every 0.2 m^2 increase in BSA, perfusion decreased by 0.07 ml/min/g. Data from allometric scaling among 4 species have shown decreasing baseline myocardial perfusion with increasing body size (literature average 6.6 ml/min/g in mice, 4.8 ml/min/g in rats, 1.0 ml/min/g in dogs, and 0.6 ml/min/g in humans) (16). Heart weight remains a near constant 0.55% of body mass among species but myocardial flow (ml/min) scales as body mass to the 0.7 exponent (namely, absolute myocardial flow increases more slowly than a constant proportion). Consequently, the literature indicates that

FIGURE 4 Normal Left Ventricular Function With Coronary Pressures From 45 to 125 mm Hg



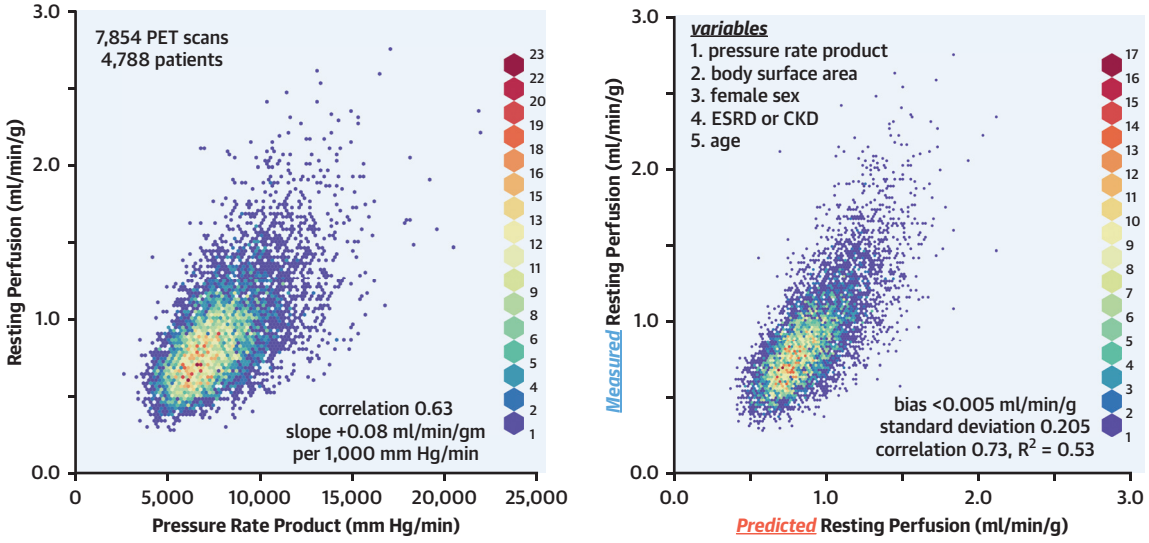
In 26 subjects with normal left ventricular function undergoing invasive coronary pressure assessment and myocardial blood flow imaging, perfusion (ml/min/g) remained intact until at least ~45 mm Hg. Reproduced with permission from Di Gioia et al. (10).

FIGURE 5 Resting Flow and Contractile Function



Animal models emphasize the close relationship between resting flow and contractile function. Almost any reduction in resting flow produces an impairment in myocardial performance. Conversely, normal ventricular function indicates intact resting flow. Reproduced with permission from Vatner (13).

FIGURE 6 Resting Perfusion by Cardiac PET



In our database of 7,854 scans from 4,788 patients or research subjects (14), baseline absolute perfusion (in ml/min/g) showed a direct relationship with pressure rate product at rest. When including pressure rate product plus the next 4 strongest parameters associated with resting perfusion, the model explained a small majority of the clinical variation with an imprecision of 0.2 ml/min/g without bias. Hexagrams indicate count density in this heatmap. CKD = chronic kidney disease; ESRD = end-stage renal disease; PET = positron emission tomography.

myocardial perfusion (ml/min/g) displays an inverse relationship with body mass. Our observation in humans is consistent with these allometric results among species, with BSA explaining an additional 15% of resting perfusion variation in our PET population.

The next strongest factor after PRP and BSA was female sex, a well-known and widely replicated observation (17), although the physiological mechanism remains unclear. Resting perfusion in women was 0.09 ml/min/g higher than in men after multivariable adjustment and explained an additional 1.6% of the variation in our cohort. Furthermore, a clinical history of chronic kidney disease, including end-stage renal disease, was associated with an 0.08 ml/min/g increase in baseline perfusion; this explains an additional 0.4% of the population-level variation and in agreement with prior, unadjusted observations (18,19), although again without an explanatory mechanism as PRP has already accounted for commonly elevated blood pressure in renal patients. Finally, age showed a very weak influence after adjustment, increasing by <0.01 ml/min/g per decade and accounting for <0.1% of the variation.

Including additional variables, although statistically significant, provided ever smaller improvements in the model. **Table 1** displays a multivariable model using just 5 straightforward parameters listed in order of importance: PRP, BSA, female sex, chronic or end-stage kidney disease, and age. When comparing the predictions from this model against observed resting perfusion, **Figure 6** indicates little bias (<0.01 ml/min/g; paired $p = 0.262$) but sizable imprecision of 0.2 ml/min/g and accounts for a thin 53% majority of the observed variation. Therefore, about one-half of resting perfusion associates with straightforward clinical parameters, although our cross-sectional analysis cannot show causality. The other one-half represents patient-specific factors that are more difficult to assess, such as contractility, preload, and the combination of afterload and preload into wall stress based on LV geometry and diverse vasoactive mechanisms inherent in endothelial function with a resulting impact on resting perfusion.

Often research publications and clinicians are tempted to "adjust" the observed resting perfusion based on the PRP. For example, current guidelines for cardiac PET perfusion advise that "adjustment of resting [myocardial blood flow] to account for changes in the heart rate-pressure product should be considered as part of the interpretation" and that "age-related increases in resting [myocardial blood flow] can be explained by rate-pressure product correction" as well as that "in individuals with advanced obesity, resting [myocardial blood flow] may also be elevated" (20). However, these

statements seem inconsistent with observed physiology because PRP only accounts for ~35% of the variation in resting perfusion, age retains its mild perfusion increase even after adjustment for PRP, and BSA shows a reduction (not an increase) in perfusion. The multivariable model in **Table 1 and Figure 6** indicates that only one-half of resting perfusion can be accounted for by using standard clinical parameters with an imprecision of 0.2 ml/min/g such that, for an individual patient, it is almost impossible to determine if the observed perfusion differs meaningfully from expectations. Although adjustments may be useful for minimizing the SD of group data (and therefore may be reasonable for a population analysis or comparison), they fail to assess or even obscure important biological differences or clinical pathophysiology in individuals (and therefore in our opinion should be minimized or used qualitatively when making clinical decisions). Furthermore, stress perfusion retains correlations with stress PRP (correlation coefficient 0.48) and BSA (correlation coefficient -0.35) and remains higher in women (+0.47 ml/min/g). Why "adjust" perfusion for these parameters at baseline but not during hyperemia?

Finally, does resting perfusion associate with clinical prognosis? The left panel in **Figure 7** displays "hard" outcomes of all-cause death, nonfatal myocardial infarction, and stroke for our large cohort of patients and research subjects undergoing absolute flow quantification using cardiac PET with long-term follow-up (14). Using resting perfusion as a time-varying covariate to account for multiple scans per person, Cox proportional hazards models showed no significant association with outcomes (hazard ratio: 1.23; 95% confidence interval: 0.85 to 1.77; p = 0.276). This result remained unchanged when limiting the analysis to subjects without a significant resting defect (<5% of the left ventricle with uptake <60% of maximum). Therefore, routine measurement of resting perfusion in a clinical population imparts no knowledge of subsequent clinical outcomes.

IMPACT OF THERAPY ON RESTING PERFUSION

We identified 188 patients in our PET database (14) who had absolute perfusion imaging before and after 213 revascularizations with either PCI or coronary artery bypass grafting. As shown in the right panel of **Figure 7**, resting perfusion averaged over the entire left ventricle did not change significantly: 0.74 ml/min/g (interquartile range [IQR]: 0.60 to 0.92 ml/min/g) before versus 0.78 ml/min/g (IQR: 0.64 to 0.93 ml/min/g) after revascularization (paired p value 0.175; mean difference -0.02; SD 0.24 ml/min/g). In contrast, hyperemic perfusion averaged over the whole left ventricle increased: 1.43 ml/min/g (IQR: 1.13 to 1.85 ml/min/g) before versus 1.65 ml/min/g (IQR: 1.31 to 2.07 ml/min/g) after revascularization (paired p value <0.001). Likewise, revascularization did not change resting relative uptake defects: percentage of the left ventricle with uptake <60% maximum was 2.5% (IQR: 0.6% to 8.0%) before versus 2.3% (IQR: 0.6% to 8.0%) after revascularization (paired p value 0.707). However, stress-induced relative uptake defects were significantly reduced before (18.0%; IQR: 4.1% to 32.4%) versus after (6.8%; IQR: 1.3% to 20.2%; paired p value <0.001) revascularization.

TABLE 1 Major Multivariable Predictors of Resting Perfusion

	Coefficient* (ml/min/g)	p Value*	t Value*	F Value†	R^2‡
(Intercept)	0.98				
PRP (per 1,000 mm Hg/min)	+0.08	<0.0001	64.5	5,470	0.353
Body surface area (per 0.2 m^2)	-0.07	<0.0001	-29.6	1,680	+0.150
Female	+0.09	<0.0001	12.8	144	+0.016
ESRD or CKD	+0.08	<0.0001	8.0	62	+0.004
Age (per decade)	< +0.01	<0.0001	4.3	19	< +0.001

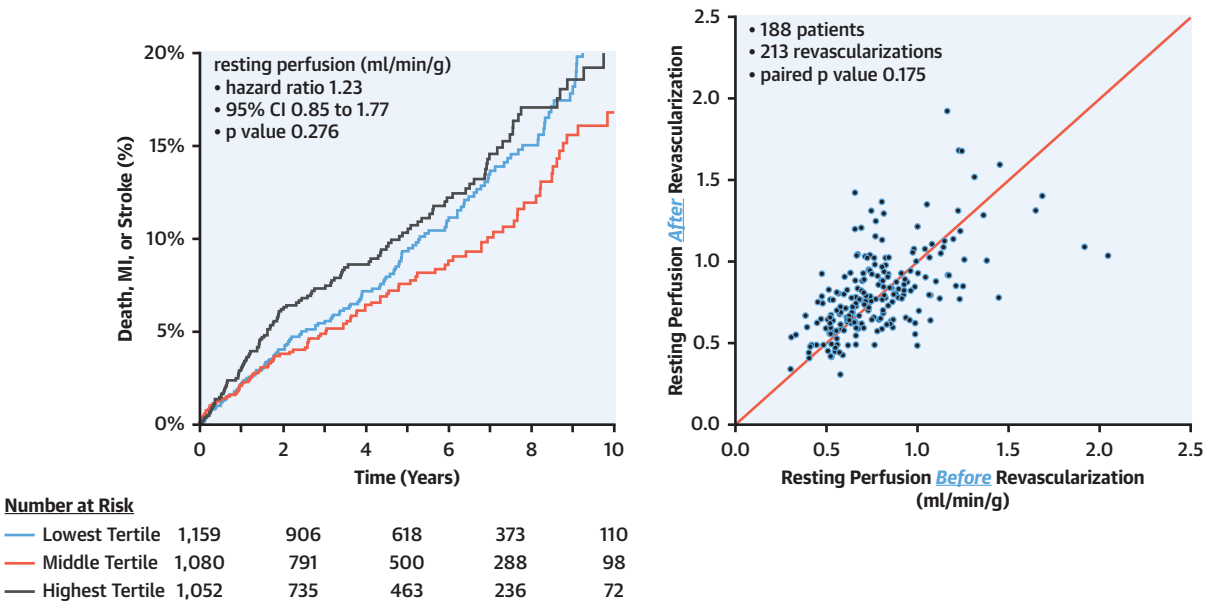
*From fixed effects of the linear mixed effects model. †Analysis of variance performed on the linear mixed effects model. ‡Cumulative changes in marginal R^2 from linear mixed effects models starting with pressure rate product (PRP) and adding each successive row.

CKD = chronic kidney disease; ESRD = end-stage renal disease.

A cohort undergoing primary PCI for ST-segment elevation myocardial infarction received thermodilution assessment of baseline coronary flow immediately after PCI (n = 86), the next day (n = 61), and after 6 months (n = 46) (21). Mean baseline transit time did not change among these 3 assessments: 0.80 s (day 0), 0.94 s (day 1), and 0.92 s (6 months) (analysis of variance, p = 0.19). However, clear infarct healing was seen via parameters such as coronary flow reserve (mean 1.8, 2.3, and 3.1 at the 3 time points; p < 0.001) and EF (44% to 48% between day 1 and 6 months in subjects with microvascular obstruction at baseline by cardiac magnetic resonance imaging).

For patients undergoing transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement for severe aortic stenosis, we might reasonably expect to observe a decrease in baseline perfusion due to the acute changes in LV filling pressures and long-term regression of LV hypertrophy. However, as summarized in our prior work (22), among 8 studies with a total of 156 vessels or subjects, only 1 series showed a decrease in resting parameters (Doppler velocity). Although the result may partially arise from the modest sample size of each cohort (generally 10 to

FIGURE 7 Clinical Prognosis and Impact of Revascularization



In our database of 3,291 patients or research subjects with adequate long-term follow-up (14), resting perfusion (in ml/min/g) averaged over the entire left ventricle did not show a significant association with all-cause death, nonfatal myocardial infarction (MI), or stroke using a Cox proportional hazards model (displayed here by tertiles of perfusion). For 188 patients who underwent 213 revascularizations with either percutaneous coronary intervention or bypass surgery, global resting perfusion did not change significantly despite clear improvements in stress flow and stress-induced relative uptake defects.

30 subjects) and therefore caution is warranted regarding effect size and potential bias, these results do not support a large effect of severe aortic stenosis on resting perfusion despite its well-known increases in afterload, filling pressures, and hypertrophy.

Together, these data show that severe coronary stenosis, healing after myocardial infarction, or severe aortic stenosis do not meaningfully affect resting perfusion, as evidenced by a lack of change after device treatment. Given the well-established benefits of revascularization and TAVR for these scenarios, the data indicate that resting perfusion cannot be used for patient selection or for monitoring the response to interventional therapy. In short, the "neutral results" described here speak to the profound ability of autoregulation to overcome even extreme pathophysiology under resting conditions. Seen another way, only by removing autoregulation (through exercise or pharmacological stress) can the impact of pathophysiology be understood.

CLINICAL IMPLICATIONS

To summarize, resting myocardial perfusion remains under the control of a large number of homeostatic mechanisms designed to maintain sufficient flow regardless of driving pressure. As a result, LV dysfunction does not arise until coronary perfusion pressure decreases to ~40 mm Hg. Straightforward clinical parameters explain approximately one-half of observed absolute resting perfusion but with wide imprecision due to biologic heterogeneity and factors such as contractility, preload, and wall stress that are not easily measured. Not only does resting perfusion not associate with clinical outcomes, it also remains unaffected by revascularization, recovery after myocardial infarction, and treating severe aortic stenosis.

These broad and consistent results from animal and human studies raise profound doubts regarding resting assessments of coronary flow and resistance to make clinical diagnostic or therapeutic decisions. Although some patients present in unstable fashion (e.g., acute myocardial infarct or cardiogenic shock) and therefore have fallen outside the bounds of autoregulation, most encounters involve patients who are clinically, hemodynamically, and electrically stable. In this large majority, autoregulation implies that resting flow measurements provide limited value regarding prognosis or response to therapy. By

contrast, hyperemic measurements show much larger changes after indicated treatment in appropriately chosen patients.

Crucially, autoregulation maintains flow while allowing pressure to vary. Resting assessments of coronary pressure have been shown to correlate with several hyperemic metrics (23), as flow generally increases with exercise or pharmacological stress, thereby augmenting pressure loss along the vessel. However, in stable patients, resting coronary pressures do not define pathology above the 40 mm Hg transition discussed earlier.

CONCLUSIONS

The clinical implication of autoregulation is that, for stable patients, resting flow, resistance, and coronary pressures above 40 mm Hg cannot exclude or diagnose disease with highly probable certainty in an individual patient, although group associations may exist.

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All authors have a patent pending on methods to correct pressure tracings from fluid-filled catheters. Drs. Johnson and Gould received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis; and have a patent pending on diagnostic methods for quantifying aortic stenosis and TAVR physiology. Dr. Johnson has received significant institutional research support from St. Jude Medical (CONTRAST; NCT02184117) and Philips Volcano Corporation (DEFINE-FLOW; NCT02328820) for other studies using intracoronary pressure and flow sensors; and has an institutional licensing and consulting agreement with Boston Scientific for the smart minimum fractional flow reserve algorithm [now commercialized under 510(k) K191008]. Dr. Gould is the 510(k) applicant for CFR Quant (K113754) and HeartSee (K143664 and K171303), software packages for cardiac PET image processing, analysis, and absolute flow quantification. Dr. De Bruyne has received institutional research grants and consulting fees from Abbott Vascular (formerly St. Jude Medical), Boston Scientific, and Opsens.

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REFERENCES

1. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. Physiol Rev 2008;88:1009–86.

2. Heusch G. Myocardial ischemia: lack of coronary blood flow, myocardial oxygen supply-demand imbalance, or what? Am J Physiol Heart Circ Physiol 2019;316:H1439–46.

3. Rubio R, Berne RM. Regulation of coronary blood flow. Prog Cardiovasc Dis 1975;18:105–22.

4. Mosher P, Ross J Jr., McFate A, Shaw RF. Control of coronary blood flow by an autoregulatory mechanism. Circ Res 1964;14:250–9.

5. Gewirtz H, Olsson RA, Brautigan DL, Brown PR, Most AS. Adenosine's role in regulating basal coronary arteriolar tone. Am J Physiol 1986;250:H1030–6.

6. Duncker DJ, Bache RJ, Merkus D. Regulation of coronary resistance vessel tone in response to exercise. J Mol Cell Cardiol 2012;52:802–13.

7. Gorman MW, Rooke GA, Savage MV, Jayasekara MP, Jacobson KA, Feigl EO. Adenine nucleotide control of coronary blood flow during exercise. Am J Physiol Heart Circ Physiol 2010;299:H1981–9.

8. Smalling RW, Kelley K, Kirkeeide RL, Fisher DJ. Regional myocardial function is not affected by severe coronary depressurization provided coronary blood flow is maintained. J Am Coll Cardiol 1985;5:948–55.

9. Canty JM Jr. Coronary pressure-function and steady-state pressure-flow relations during autoregulation in the unanesthetized dog. Circ Res 1988;63:821–36.

10. Di Gioia G, Melin JA, De Bruyne B. Coronary autoregulatory plateau in humans. J Am Coll Cardiol 2020;76:1270–1.

11. Heyndrickx GR, Millard RW, McRitchie RJ, Maroko PR, Vatner SF. Regional myocardial functional and electrophysiological alterations after brief coronary artery occlusion in conscious dogs. J Clin Invest 1975;56:978–85.

12. Marshall RC, Tillisch JH, Phelps ME, et al. Identification and differentiation of resting myocardial ischemia and infarction in man with positron computed tomography, 18F-labeled fluorodeoxyglucose and N-13 ammonia. Circulation 1983;67:766–78.

13. Vatner SF. Correlation between acute reductions in myocardial blood flow and function in conscious dogs. Circ Res 1980;47:201–7.

14. Gould KL, Johnson NP, Roby AE, et al. Regional, artery-specific thresholds of quantitative myocardial perfusion by PET associated with reduced myocardial infarction and death after revascularization in stable coronary artery disease. J Nucl Med 2019;60:410–7.

15. Baller D, Bretschneider HJ, Hellige G. Validity of myocardial oxygen consumption parameters. Clin Cardiol 1979;2:317–27.

16. Lindstedt SL, Schaeffer PJ. Use of allometry in predicting anatomical and physiological parameters of mammals. Lab Anim 2002;36:1–19.

17. Patel MB, Bui LP, Kirkeeide RL, Gould KL. Imaging microvascular dysfunction and mechanisms for female-male differences in CAD. J Am Coll Cardiol Img 2016;9:465–82.

18. Charytan DM, Skali H, Shah NR, et al. Coronary flow reserve is predictive of the risk of cardiovascular death regardless of chronic kidney disease stage. Kidney Int 2018;93:501–9.

19. Päivärinta J, Metsärinne K, Löyttyniemi E, et al. Myocardial perfusion reserve of kidney transplant patients is well preserved. EJNMMI Res 2020;10:9.

20. Murthy VL, Bateman TM, Beanlands RS, et al. Clinical quantification of myocardial blood flow using PET: joint position paper of the SNMMI Cardiovascular Council and the ASNC. J Nucl Med 2018;59:273–93.

21. Cuculi F, De Maria GL, Meier P, et al. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. J Am Coll Cardiol 2014;64:1894–904.

22. Zelis JM, Tonino PAL, Johnson NP. Why can fractional flow reserve decrease after transcatheter aortic valve implantation? J Am Heart Assoc 2020;9:e04905.

23. Hwang D, Jeon KH, Lee JM, et al. Diagnostic performance of resting and hyperemic invasive physiological indices to define myocardial ischemia: validation with 13N-ammonia positron emission tomography. J Am Coll Cardiol Intv 2017;10:751–60.

24. Duncker DJ, Merkus D. Regulation of coronary blood flow: effect of coronary artery stenosis. Arch Mal Coerce Visas 2004;97:1244–50.

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