Central intravenous administration of adenosine at a constant rate is the recommended method to induce coronary hyperemia for fractional flow reserve (FFR) assessment because it enables a steady hyperemic state. Intravenous adenosine produces vasodilatation in coronary and noncoronary vascular beds, which typically decreases mean blood pressure (BP) a –10% to –15% during stable hyperemia. Nevertheless, observational and experimental studies have observed a large interpatient variability in the BP response to intravenous adenosine, with most patients developing mild hypotension, whereas in others, BP profoundly decreases during stable hyperemia. The possible relevance of these varying BP responses to intravenous adenosine for stenosis assessment with FFR, however, has been barely addressed in the literature. Accordingly, in the present study, we investigated the relationship between adenosine-induced hypotension and clinical and intracoronary physiological measurements in an unselected series of patients with epicardial stenoses suitable for physiological interrogation, in which FFR, coronary flow reserve (CFR), and index of microcirculatory resistance (IMR) were measured.

Background—Intravenous adenosine infusion produces coronary and systemic vasodilatation, generally leading to systemic hypotension. However, adenosine-induced hypotension during stable hyperemia is heterogeneous, and its relevance to coronary stenoses assessment with fractional flow reserve (FFR) remains largely unknown.

Methods and Results—FFR, coronary flow reserve, and index of microcirculatory resistance were measured in 93 stenosed arteries (79 patients). Clinical and intracoronary measurements were analyzed among tertiles of the percentage degree of adenosine-induced hypotension, defined as follows: \( \% \Delta P_a = \left( \frac{100 \times (\text{hyperemic aortic pressure})}{\text{baseline aortic pressure}} \right) - 1 \). Overall, \( \% \Delta P_a \) was \(-13.6 \pm 12.0\%\). Body mass index was associated with \( \% \Delta P_a \) \( (r=0.258; P=0.025) \) and obesity, an independent predictor of profound adenosine-induced hypotension (tertile 3 of \( \% \Delta P_a \); odds ratio, 3.95 [95% confidence interval, 1.48–10.54]; \( P=0.006 \)). \% \Delta P_a \) was associated with index of microcirculatory resistance \( (r=0.311; P=0.002) \), coronary flow reserve \( (r=–0.246; P=0.017) \), and marginally with FFR \( (r=0.203; P=0.051) \). However, index of microcirculatory resistance \( (\beta=0.003; P<0.001) \) and not \% \Delta P_a \) \( (\beta=–0.001; P=0.564) \) was a predictor of FFR. Compared with tertiles 1 and 2 of \% \Delta P_a \) \( (n=62 \ [66.6\%]) \), stenoses assessed during profound adenosine-induced hypotension \( (n=31 \ [33.3\%]) \) had lower index of microcirculatory resistance \( (12.4 \ [8.6–22.7] \text{ versus} \ 20 \ [15.8–35.5]; P=0.001) \) and FFR values \( (0.77 \pm 0.13 \text{ versus} \ 0.83 \pm 0.12; P=0.021) \), as well as a nonsignificant increase in coronary flow reserve \( (2.5 \pm 1.1 \text{ versus} \ 2.2 \pm 0.87; P=0.170) \).

Conclusions—The modification of systemic blood pressure during intravenous adenosine infusion is related to hyperemic microcirculatory resistance in the heart. Profound adenosine-induced hypotension is associated with obesity, lower coronary microcirculatory resistance, and lower FFR values.

Key Words: adenosine • coronary disease • physiology
WHAT IS KNOWN

- Intravenous adenosine infusion produces coronary and systemic vasodilatation, generally leading to systemic hypotension.
- Although adenosine-induced hypotension is known to be heterogeneous, its relevance to coronary stenoses assessment with fractional flow reserve (FFR) remains largely unknown.

WHAT THE STUDY ADDS

- The modification of systemic blood pressure during adenosine infusion is related to the hyperemic microcirculatory resistance in the heart.
- Profound adenosine-induced hypotension is associated with obesity, lower coronary microcirculatory resistance, and lower FFR values.

(IMR) were measured during their clinical evaluation in the catheterization laboratory.

Methods

Study Population

Patients with a clinical indication for FFR interrogation of ≥1 vessels showing an intermediate stenoses (40%–70% diameter stenosis by quantitative coronary angiography) were enrolled in the Hospital Clinico San Carlos, Madrid, Spain, and the Maastricht University Medical Center, Maastricht, The Netherlands. The filmed guide catheter filled with coronary nitrates (0.2 mg). Offline quantitative coronary angiography software (CASS II, Pie Medical, Maastricht, The Netherlands). The filmed guide catheter filled with contrast medium was used as a calibrating device. Minimum lumen diameter, percent diameter stenosis, lesion length, and reference lumen diameter were measured. Data were collected by 2 experienced reviewers blinded to physiological data.

Intracoronary Physiological Indices

Coronary guidewires equipped with sensors of pressure and temperature (St Jude Medical, St. Paul, MN) were used according to described methodologies. FFR was calculated as the ratio of distal coronary pressure (Pd) to proximal coronary pressure (Pa) at stable hyperemia induced by intravenous adenosine (140 μg/kg per minute through a central vein). Persistence of calibration was checked. CFR was measured simultaneously with FFR using the thermodilution method. Resting and hyperemic thermodilution curves (in triplicate) were obtained, and CFR was calculated as the ratio of mean tran-stime (Tmnbas) divided by mean hyperemic transit time (Tmn hyp). Persistence of calibration was checked. CFR was calculated as the ratio of mean distal coronary pressure during stable hyperemia and Tmn = 100(Pd-hyp×100/Pa-bas).

Variations in mean Aortic BP Produced by Adenosine

Mean aortic (P) and distal (Pd) pressures were measured with the guiding catheter and the coronary guidewire at rest (P_min and P_min) and during stable hyperemia (P_max and P_max). The adenosine-induced absolute (ΔP) and percentage BP change (%ΔP) was calculated as follows: ΔP=−(P_min−P_max) and %ΔP=−100×(P_max×100/P_min).

Cutoff Values

FFR ≤ 0.80 (low FFR) and CFR < 2 (low CFR) were used as threshold values. The adenosine-induced hypotension was analyzed across tertiles of %ΔPa and labeled as mild, moderate, and profound hypotensive responses (first, second, and third tertile, respectively). Based on the reported variability of IMR in patients with and without coronary artery disease, values of IMR ≥ 30 U were assumed abnormal (high IMR).

Statistical Analysis

All continuous variables are presented as mean±SD or median (interquartile range) according to their normal or non-normal distribution. Categorical variables are presented as counts and percentages. Normality and homogeneity of the variances were tested using the Kolmogorov–Smirnov and Levene tests. Data were analyzed on a per-patient basis for clinical characteristics and on a per-vessel basis for the rest of calculations. Patients with discrepancies in %ΔPa between interrogated vessels were excluded from per-patient analyses. For the purposes of analysis, vessels within the same patient were assumed to be independent. Continuous variables were compared with independent or paired t tests or Mann–Whitney U tests, as appropriate. Categorical variables were compared by the Fisher exact test. Differences in variables across decreasing tertiles of %ΔPa were compared with 1-way ANOVA, Kruskal–Wallis, or Fisher exact test. Differences in variables across decreasing tertiles of %ΔPa were compared with 1-way ANOVA, Kruskal–Wallis, or Fisher exact test, followed by Tukey, Games–Howell, or Fisher post hoc test, as appropriate. After the inspection of the data, the combination of tertiles 1 and 2 was considered because the third tertile %ΔPa showed differences with respect to the others in terms of IMR and FFR values. Therefore, the former tertile was also compared with tertiles 1 and 2 using t tests, Mann–Whitney U test, or Fisher exact test, as appropriate. Tests of linear trend across decreasing tertiles of %ΔPa (polynomial contrasts for continuous and Mantel–Haenszel tests for categorical variables) were conducted. Correlation coefficients (Pearson r or Spearman ρ) between quantitative variables were also calculated. Multivariable linear regression analyses, including %ΔPa and microcirculatory resistance, were used to determine predictors of FFR. Binary logistic regression analysis in both univariable and multivariable models was used to identify clinical predictors of adenosine-induced hypotension. Models were constructed using the backward selection algorithm, considering as the set of possible covariates all variables with a P<0.10. Differences were considered significant at P<0.05 (2-sided). The SPSS version 20.0 (IBM Corp, Armonk, NY) statistical software package was used for all calculations.

Results

Baseline Characteristics

Clinical characteristics of the study population (93 arteries studied in 79 patients) are shown in Table 1. Overall, P_min was 90±18 mm Hg and fell to 78±20 mm Hg (P_max) during stable hyperemia (P<0.001). Thus, adenosine produced a decrease in BP (ΔP) of −12±11 mm Hg (min–max, +13 to −48 mm Hg) that corresponded to a percentage fall (%ΔP) of −13.6±12% (min–max, +13.3% to −45.7%; Figure 1). A
tertile analysis according to $\%\Delta P_a$ is also shown in Table 1. Values of $–6.7\%$ and $–17.2\%$ defined the $\%\Delta P_a$ tertiles. Body mass index was associated with $\%\Delta P_a$ ($r=–0.236; \ P=0.037$), and a statistical trend toward higher drops in BP ($\%\Delta P_a$) was observed in patients with obesity (body mass index $\geq 30$ kg/m$^2$; $–16.9±12.1\%$ versus $–11.4±12\%; \ P=0.056$). Compared with tertiles 1 and 2 of $\%\Delta P_a$ (n=49), patients experiencing profound hypotensive responses (tertile 3 of $\%\Delta P_a$; n=25) were more likely to be diabetic (44% versus 18.4%; $\ P=0.021$) and obese (60% versus 28.6%; $\ P=0.009$). Although diabetes mellitus and dyslipidemia were statistically associated with profound hypotensive responses in univariate analyses, obesity remained as its only independent predictor (odds ratio [OR], 3.95 [95% confidence interval {CI}: 1.48–10.54]; $\ P=0.006$).

Of note, the used adenosine dosage was not statistically associated with $\%\Delta P_a$ ($r=0.173; \ P=0.128$).

Relationship Between Adenosine-Induced Hypotension and FFR
Angiographic and physiological characteristics of studied vessels are found in Table 2. Neither quantitative coronary angiography analyses, baseline pressures, nor the hyperemic trans-stenotic pressure gradient ($P_{\text{a-hyp}}$/$P_{\text{d-hyp}}$; $r=0.086; \ P=0.412$) was associated with $\%\Delta P_a$. Furthermore, FFR was not statistically associated with $P_{\text{a-hyp}}$ ($r=–0.077; \ P=0.461$) or $P_{\text{d-hyp}}$ ($r=–0.159; \ P=0.127$). However, a trend toward a significant association between FFR and $\%\Delta P_a$ ($r=0.203; \ P=0.051$) was observed, suggesting a relationship between the degree of adenosine-induced hypotension and hyperemic coronary hemodynamics. This association became stronger when stenoses assessed during profound hypotensive responses (n=31) were compared with those in tertiles 1 and 2 of $\%\Delta P_a$ (n=62), because during the former, FFR values were significantly lower (0.77±0.13 versus 0.83±0.12; $\ P=0.021$).
and more likely to be below the ≤0.80 cutoff (61.3% versus 32.3%; \( P = 0.008 \); Figure 2A). Furthermore, a trend in the prevalence of FFR values ≤0.80 across decreasing tertiles of \( \% \Delta P_a \) was observed (\( P \) for trend=0.041), changing from 35.5% (OR=1) to 29.0% (OR=0.744; 95% CI: 0.255–2.166) and 61.3% (OR, 2.879; 95% CI: 1.026–8.074) from the first to the second and third tertiles of \( \% \Delta P_a \), respectively, without a significant deviation from linearity (\( P = 0.073 \); Table 2). Finally, the \( \% \Delta P_a \) observed during the assessment of stenoses with FFR ≤0.80 (n=39) was significantly higher than in those with FFR >0.80 (n=54; –17.1±11.9% versus –11.0±11.6%; \( P = 0.014 \)).

Table 2. General Characteristics of Epicardial Stenoses Included in the Study According to Adenosine-Induced Hypotensive Effect

<table>
<thead>
<tr>
<th>Stenosis location</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending artery</td>
<td>40 (43.0)</td>
<td>14 (45.2)</td>
<td>13 (41.9)</td>
</tr>
<tr>
<td>Circumflex</td>
<td>21 (22.6)</td>
<td>8 (25.8)</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>32 (34.4)</td>
<td>9 (29)</td>
<td>12 (38.7)</td>
</tr>
</tbody>
</table>

Quantitative coronary angiography

| Reference diameter, mm | 3.06±0.64 | 3.05±0.75 | 2.91±0.59 | 2.80±0.70 | 0.380 |
| Minimal lumen diameter, mm | 1.30±0.43 | 1.26±0.52 | 1.33±0.35 | 1.30±0.42 | 0.857 |
| Diameter stenosis, % | 48±13 | 50±13 | 47±10 | 48±12 | 0.693 |
| Lesion length, mm | 8.0±3.7 | 8.1±4.4 | 7.8±2.9 | 7.1±3.2 | 0.593 |

Physiological parameters

| \( \% \Delta P_a, \% \) | –13.6±12.0 | –0.9±5.5† | –13.1±2.8 | –26.7±7.8†† | <0.001§ |
| \( \Delta P_a, \text{mm Hg} \) | –12±11 | –1±5† | –12±3 | –23±7†† | <0.001§ |
| \( P_{a-bas}, \text{mm Hg} \) | 90±18 | 93±19 | 88±13 | 89±22 | 0.552 |
| \( P_{a-hyp}, \text{mm Hg} \) | 81±18 | 84±21 | 80±13 | 78±21 | 0.386 |
| \( P_{a-bas}/P_{a-hyp}, \text{mm Hg} \) | 0.91 (0.88–0.95) | 0.93 (0.89–0.96) | 0.91 (0.90–0.96) | 0.90 (0.86–0.94) | 0.350 |
| \( P_{d-bas}, \text{mm Hg} \) | 6.0±11 | 6.0±11 | 6.0±11 | 5.9±11 | 0.126 |
| \( P_{d-hyp}, \text{mm Hg} \) | 5.1±10 | 5.1±10 | 5.1±10 | 5.1±10 | 0.126 |
| \( P_{d-bas}/P_{d-hyp}, \text{mm Hg} \) | 1.3±0.8 | 1.3±0.8 | 1.3±0.8 | 1.3±0.8 | 0.126 |
| FFR | 0.81±0.12 | 0.82±0.13 | 0.84±0.10 | 0.77±0.13 | 0.058 |
| FFR ≤0.80 | 39 (41.9) | 11 (35.5) | 9 (29.0) | 19 (61.3)† | 0.033§ |
| FFR <0.75 | 22 (23.7) | 6 (19.4) | 3 (9.7) | 13 (41.9)† | 0.011§ |
| CFR | 2±0.80 | 2±0.7 | 2.4±1 | 2.5±1.2 | 0.132 |
| CFR <2 | 42 (45.2) | 16 (51.6) | 14 (45.2) | 12 (38.7) | 0.635 |
| Corrected IMR, U | 16.0 (12.1–23.5) | 19.0 (12.1–40.8) | 26.4 (16.8–29.1) | 12.7 (6.7–22.7)†† | 0.003 |
| Uncorrected IMR, U | 19.5 (12.7–30.3) | 22.0 (16.0–42.0) | 22.0 (16.0–29.0) | 12.8 (10.0–23.0)†† | 0.002 |
| Corrected IMR ≥30 U | 21 (22.6) | 12 (38.7) | 7 (22.6) | 2 (6.5)†† | 0.010§ |
| Uncorrected IMR ≥30 U | 23 (24.7) | 12 (38.7) | 7 (22.6) | 4 (9.7)†† | 0.019§ |
| Tmnbas, seg | 0.73±0.49 | 0.76±0.49 | 0.82±0.52 | 0.60±0.44 | 0.184 |
| Tmnhyp, seg | 0.37±0.21 | 0.38±0.21 | 0.41±0.26 | 0.32±0.13 | 0.192 |

Values are mean±SD, median (25th–75th), or n (%). CFR indicates coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; \( P_{a-bas} \), aortic pressure (baseline); \( P_{a-hyp} \), aortic pressure (hyperemia); \( P_{d-bas} \), distal pressure (baseline); \( P_{d-hyp} \), distal pressure (hyperemia); Tmnbas, basal mean transit time; and Tmnhyp, hyperemic mean transit time.

†\( P<0.05 \) compared with tertile 2.
‡\( P<0.05 \) compared with tertile 1.
§\( P<0.05 \) for linear trend.

Relationship Among Adenosine-Induced Hypotension, Microcirculatory Resistance, and CFR

A significant association between IMR and \( \% \Delta P_a \) (\( \rho = 0.311; \ P = 0.002 \)) was observed, suggesting a proportionality between the change in systemic arterial resistance and minimum microcirculatory resistance produced by adenosine infusion (Figure 3). Furthermore, stenoses assessed during profound hypotensive responses (n=31; Figure 2B) had significantly lower IMR values than those assessed in tertiles 1 and 2 of \( \% \Delta P_a \) (n=62; 12.7 [8.7–22.7] versus 20 [15.8–35.5]; \( P = 0.001 \)). A decreasing trend in the prevalence of high IMR values...
(≥30 U) across tertiles of %ΔPa was also observed (P for trend=0.0025), decreasing from 38.7% (OR=1.0) to 22.6% (OR, 0.462 [95% CI: 0.152–1.401]) and 6.5% (OR, 0.109 [95% CI: 0.022–0.543]) from the first to the second and third tertiles of %ΔPa, respectively, without a significant deviation from linearity (P=0.752). Of note, the %ΔPa observed during the assessment of stenoses with IMR ≥30 (n=21) was significantly lower than in those with IMR <30 (n=72; –5.7±9.8% versus –15.9±11.7%; P<0.001). CFR was also associated with %ΔPa (r=–0.246; P=0.017), and although stenoses assessed during profound hypotensive responses had higher values of CFR than those assessed in tertiles 1 and 2 of %ΔP, (2.5±1.5 versus 2.2±0.9), statistical significance was not reached (P=0.170). However, the observed increase in CFR under profound hypotensive responses seemed to be clinically relevant, because during the latter, the prevalence of vessels with FFR ≤0.80 and CFR >2 was higher (35.5% versus 14.5% in tertiles 1 and 2 of %ΔPa; P=0.031; OR, 3.24 [95% CI: 1.17, 8.99]; P=0.023).

Integrating Adenosine-Induced Hypotension, FFR, Microcirculatory Resistance, and CFR

Because IMR and %ΔP were significantly associated with FFR (at P<0.10), multivariable regression models were performed. These analyses identified that IMR (β=0.003; P<0.001) and not %ΔP (β=0.001; P=0.564) was independently associated with FFR. Finally, Figure 4 summarizes the hemodynamic findings of the present study: although no significant differences were observed between stenoses assessed during mild and moderate adenosine-induced hypotensive responses, those stenoses assessed during profound adenosine-induced hypotension had significantly lower IMR and FFR values, as well as a nonsignificant increase in CFR.

Discussion

To our knowledge, this is first study that investigated differences in the functional assessment of coronary stenoses among different degrees of adenosine-induced hypotension. Our results suggest that such response is heterogeneous and associated with relevant differences in clinical and intracoronary physiological characteristics. We observed that adenosine-induced hypotension was associated with body mass index and more pronounced in obese subjects. We also observed a proportionality between the modification in systemic arterial and coronary microcirculatory resistance produced by intravenous adenosine. Finally, the obtained FFR values were
associated with microcirculatory resistance, with FFR and IMR being lower in those stenoses assessed during profound hypotensive responses. In the following paragraphs, we discuss the potential clinical implications of our observations in the context of current knowledge of adenosine physiology.

Coronary and Systemic Effects of Adenosine Infusion

The most widely recommended coronary hyperemic agent is intravenous adenosine because of its safety and ability to produce a steady hyperemic state. Physiologically, adenosine is an endogenous purine nucleoside that interacts with specific cell surface receptors located on smooth muscle and endothelial cells. These receptors can be divided into 4 major subtypes: $A_1$, $A_{2A}$, $A_{2B}$, and $A_3$. Adenosine receptors are coupled to G proteins that modulate the activity of adenylate cyclase in different directions: $A_1$ and $A_3$ receptors are coupled to $G_i/G_O$ proteins that inhibit adenylate cyclase activity, whereas $A_{2A}$ and $A_{2B}$ receptors are coupled to $G_s$ that activates adenylate cyclase. When activated, adenylate cyclase leads to the production and accumulation of cAMP that activates protein kinase A, which ultimately produces smooth muscle cell hyperpolarization and relaxation, particularly through the activation of intermediate-conductance $K_{Ca}$ channels.

Therefore, adenosine-induced peripheral and coronary dilatation is mainly mediated through the activation of $A_{2A}$ and $A_{2B}$ receptors. However, on the other side, it has been consistently observed that the inhibition of adenylate cyclase (mediated by the $A_1$ and $A_3$ receptors) leads to vasoconstriction. By being the natural agonist, adenosine is able to activate all 4 receptors ($A_1$, $A_{2A}$, $A_{2B}$, and $A_3$). Thus, by virtue of differential coupling to either $G_s$ ($A_{2A}$ and $A_{2B}$) or $G_i$ proteins ($A_1$ and $A_3$), adenosine is capable to elicit both dilatation ($A_{2A}$- and $A_{2B}$-mediated) and constriction ($A_1$- and $A_3$-mediated) in the peripheral and coronary vascular territories.

In the systemic circulation, intravenous adenosine produces a dose-dependent decrease in vascular resistance that is normally paralleled by significant decreases in central venous and left ventricular end-diastolic pressures. Although a reflex sympathetic discharge is also produced (aimed to increase cardiac output), in clinical practice, it is accepted that intravenous adenosine decreases mean BP –10% to –15% during FFR measurements. Interestingly, however, heterogeneous responses in BP to intravenous adenosine have been reported in observational and experimental settings, ranging from hypertensive to profound hypotensive. Notwithstanding, the possible clinical significance of this heterogeneous BP response to intravenous adenosine for FFR measurement has been barely addressed in previous research.

Profound Adenosine-Induced Hypotension and Its Relationship With Obesity

Profound hypotension secondary to adenosine infusion has been related to some pathologies and has been attributed to an inadequate increase in cardiac output because of sympathetic autonomic dysfunction. Interestingly, consistent evidence links obesity with sympathetic autonomic dysfunction, and hyperinsulinemia has been proposed as the underlying mechanism. Hyperinsulinemia simultaneously increases sympathetic activity, desensitizes the baroreflex, increases cardiac output, and induces peripheral vasodilatation. Although this is partly the consequence of an expanded body mass, regional hemodynamic studies have observed that limb vascular resistances are either normal or decreased in normotensive obese individuals. Therefore, obesity has been considered a chronic high-output, low-resistance state. Under such conditions, it seems reasonable to speculate that adenosine-induced hypotension could be increased. Another possible explanation for this observation comes from recent insights on adenosine physiology because some pathological states have been...
associated with an heterogeneous impairment in adenosine receptor subtypes. Specifically, it has been proposed that in conditions where \( \alpha_1 \) receptor-mediated responses are preserved but \( \beta_1 \) receptor-mediated responses are impaired, an increase in adenosine-induced dilatation can be produced because of diminished \( \alpha_1 \) constrictive effects. Obe- sity is one of these conditions. \( \alpha_1 \) receptor agonists are less potent in obese animals, and the concentration of \( \alpha_1 \) receptors is lower in adipocytes isolated from obese humans compared with nonobese. Furthermore, the decrease in these receptors, which is attributed to downregulation, is negatively correlated with body mass index. Although the translation of these findings from the adipose to the vascular tissue is speculative, proportional changes in subtypes of adenosine receptors among different human tissues have been observed, providing biological plausibility to this hypothesis. Taken all together, our observation is supported by available information that suggests that obesity might be related to profound hypotensive responses to intravenous adenosine either through an impaired sympathetic autonomic or possibly through an impaired adenosine \( \alpha_1 \) receptor function.

Assessment of Coronary Stenoses During Different Degrees of Adenosine-Induced Hypotension

Coronary hemodynamics are influenced by shifting systemic (aortic) and intraventricular pressures, and the coronary perfusion pressure is a result of the difference between diastolic \( P_d \) and left ventricular end-diastolic pressure. Challenging the proposal that FFR remains unaltered in shifting hemodynamic conditions, Siebes et al observed in a resistive model that for a given coronary stenosis, FFR increased with decreasing \( P_d \) or increasing microcirculatory resistance. At a low driving pressure, such as that observed in our patients with profound hypotensive responses, FFR should be higher if predominantly dependent on aortic pressure. For this reason, it could result paradoxical that in our work, stenoses interrogated during profound hypotensive responses presented significantly lower FFR values. However, this can be explained by a novel observation in our work, namely that microcirculatory resistance significantly decreases as adenosine hypotensive effect becomes larger (Figure 3). From a hemodynamic point of view, these findings remain congruent with the work of Siebes et al because these authors also observed resistive changes in the microcirculation as determinants of final FFR values with varying driving pressures.

It remains uncertain whether the marked fall in microcirculatory resistance in patients with profound hypotensive responses to intravenous adenosine obeys to an exacerbated response to adenosine—potentially triggered by impaired sympathetic autonomic or adenosine \( \alpha_1 \) receptor function—or a decrease in zero flow pressure as a result of decreased left ventricular end-diastolic pressure, which has been reported to influence FFR interrogation. Nevertheless, the potential contribution of this phenomenon to overestimation of coronary stenosis severity is supported by the obtained CFR measurements in our study because the observed proportion of vessels with CFR values >2 despite FFR ≤0.80 was significantly higher during profound hypotensive responses. This is of particular relevance because it has been proposed that patients in this quadrant of the FFR-CFR classification should not be treated on the grounds of documented preserved myocardial flow. Similarly, the fact that the number of perfusion defects was not larger in patients who developed profound hypotension during intravenous adenosine in a previous myocardial perfusion imaging study suggests that this phenomenon might selectively affect pressure-derived indices such as FFR.

Limitations

Our study has several limitations. First, our relatively small sample size is a limitation when drawing conclusions, and our findings should be interpreted as exploratory and hypothesis generating. Second, coronary collateral wedge pressure was not measured in our study. Although the inclusion of the latter pressure in the calculation of microcirculatory resistance is currently a subject of important debate, it has recently been observed that if this pressure is not considered when microcirculatory resistance is calculated with the thermodilution method, IMR might be overestimated. However, other authors who used Doppler velocity to measure coronary flow have observed that the incorporation of wedge pressure as an estimated contribution of collateral blood flow does not substantially influence the assessment of coronary microcirculatory resistance when FFR >0.6. Being aware of the current debate and to minimize a potential methodological error, we decided to correct IMR values when FFR <0.75 using the regression equation derived by Yong et al for this purpose. However, a separate analysis of our data set using uncorrected values of IMR (Table 2) revealed similar results to those reported in the article, suggesting that this correction had little effects in our findings.

Acknowledgments

Dr Echavarria-Pinto acknowledges the Fundació Interhospitalaria Investigación Cardiovascular, Madrid, Spain, for a clinical/research scholarship. We acknowledge Professor S. Jamal Mustafa (Department of Physiology and Pharmacology, West Virginia University, Morgantown, WV) for his kind review of the manuscript.

Disclosures

Dr Escaned has served as speaker in educational events organized by St. Jude Medical and Volcano Corporation. Dr Davies is a consultant for Volcano Corporation. The other authors report no conflicts.

References

Low Coronary Microcirculatory Resistance Associated With Profound Hypotension During Intravenous Adenosine Infusion: Implications for the Functional Assessment of Coronary Stenoses

Mauro Echavarria-Pinto, Nieves Gonzalo, Borja Ibañez, Ricardo Petraco, Pilar Jimenez-Quevedo, Sayan Sen, Sukkinder Nijjer, Jason Tarkin, Fernando Alfonso, Ivan J. Núñez-Gil, Camino Bañuelos, Alicia Quirós, Antonio Fernández-Ortiz, Carlos Macaya, Bon-Kwon Koo, Justin Davies and Javier Escaned

Circ Cardiovasc Interv. published online January 7, 2014;
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/early/2014/01/07/CIRCINTERVENTIONS.113.000659

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org/subscriptions/