Supplementary Information: Sensitivity Analysis

1. Microvascular Resistance Local Sensitivity Analysis

To evaluate the robustness of the virtual FFR model with respect to variations in microvascular resistance, a local sensitivity analysis was performed following standard approaches in the literature.

1.1 Method

Microvascular resistance was perturbed by ±3% and ±6% around a baseline value. By combining these perturbations with the presence or absence of a guide wire, a total of 10 cases were evaluated (see Table S1). Normalized sensitivity indices were calculated for each perturbation according to:

$$S_{ij} = \frac{(y_i^+ - y_i^-)/\bar{y}_i}{2 \times \Delta P} \tag{1}$$

where y_i^+ and y_i^- are the FFR values at $+\Delta P$ and $-\Delta P$ perturbations, respectively, $\bar{y}_i = 0.5(y_i^+ + y_i^-)$ is the mean FFR, and ΔP represents the fractional perturbation (0.03 or 0.06).

1.2 Result and Analysis

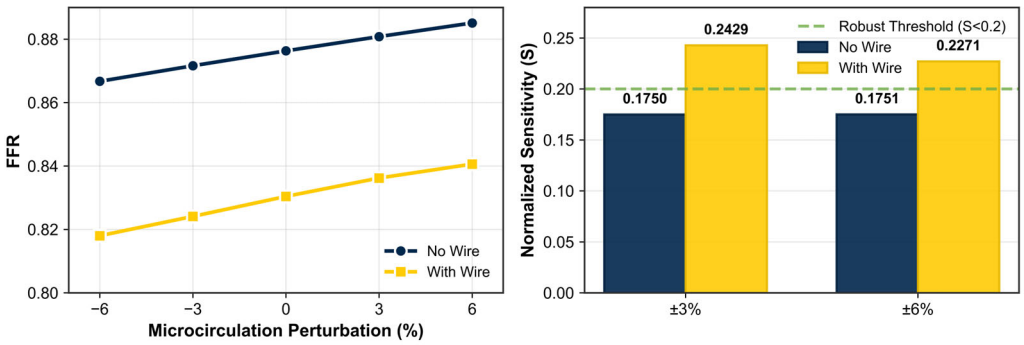
Table S1. FFR values under each perturbation condition.

Perturbation(%)	No Wire	With Wire
-6	0.867	0.818
-3	0.872	0.824
0	0.876	0.830
3	0.881	0.836
6	0.885	0.841

Normalized sensitivity indices for ±3% and ±6% Microvascular perturbations are presented in Table S2.

Table S2. Normalized sensitivity indices

Perturbation	No Wire	With Wire
±3%	0.1750	0.2429
±6%	0.1751	0.2271
Mean	0.1751	0.2350



(a) **(b)**

Figure S1: Sensitivity analysis of wire influence and microcirculation perturbation in FFR: (a) FFR value;(b) Normalized sensitivity indices

Figure S1(a) shows the FFR values under different microvascular resistance perturbations, with and without a guide wire. The FFR values range from 0.818 to 0.885 across all cases, and are consistently lower in the presence of a guide wire at each perturbation level.

The corresponding normalized sensitivity indices are presented in Figure S1(b). The values remain below 0.2 without a guide wire and slightly exceed 0.2 in the presence of a guide wire. Across both perturbation magnitudes, the sensitivity indices are consistently higher with a guide wire than without. These results indicate that the model exhibits good robustness to physiologically plausible variations in microvascular resistance.

2. Variance-Based Global Sensitivity Analysis of Stenosis Severity and Pressure Wire Effects

To quantify the relative contributions of stenosis severity and pressure wire

presence to the variability of FFR, a variance-based global sensitivity analysis was performed.

2.1 Method

Let the model output be defined as:

$$Y = f\left(X_1, X_2\right) \tag{2}$$

where: Y is the predicted FFR, X_1 denotes stenosis severity, X_2 denotes pressure wire status (binary variable: 0 = no wire, 1 = wire).

Variance-based sensitivity analysis was performed to quantify the contributions of input variables to FFR variability. The total variance of the model output was decomposed as:

$$\mathrm{Var}(Y) = V_1 + V_2 + V_{12} \tag{3}$$

where V_1 and V_2 represent the main effects of stenosis severity and pressure wire presence, respectively, $V_1 = V\left[E\left(Y \mid X_1\right)\right]$, $V_2 = V\left[E\left(Y \mid X_2\right)\right]$ and V_{12} denotes their interaction effect.

First-order sensitivity indices were calculated as:

$$S_1 = \frac{V_1}{V_1 + V_2 + V_{12}}, \quad S_2 = \frac{V_2}{V_1 + V_2 + V_{12}} \tag{4}$$

which quantify the individual contributions of each factor.

To further account for interaction effects, total-effect sensitivity indices were computed as:

$$S_{T1} = \frac{V_1 + V_{12}}{\mathrm{Var}(Y)}, \quad S_{T2} = \frac{V_2 + V_{12}}{\mathrm{Var}(Y)} \tag{5}$$

representing the overall contribution of each variable, including both main and interaction effects.

2.2 Result and Analysis

The computed FFR values under varying stenosis severity and wire conditions

are summarized in Table S3.

Table S3. FFR values under varying stenosis severity and wire conditions

Stenosis (%)	No Wire	Wire	Delta FFR
0	0.910	0.883	0.027
20	0.909	0.880	0.029
40	0.906	0.875	0.030
60	0.885	0.846	0.039
70	0.846	0.794	0.052
75	0.809	0.743	0.066
80	0.735	0.629	0.106
85	0.634	0.373	0.261

The variance-based sensitivity analysis of FFR are summarized in Table S4.

Table S4. Variance-based sensitivity analysis of FFR

Component	Variance Contribution	First-order Index (S)	Total-effect Index (ST)
Stenosis severity (X_1)	0.0166	0.854	0.924
Pressure wire (X_2)	0.00148	0.076	0.146
Interaction	0.00136	–	–
Total	**0.0194**	–	–

Variance contributions and sensitivity indices were calculated based on variance decomposition of model outputs. First-order indices represent main effects, while total-effect indices include both main and interaction effects.

The variance-based global sensitivity analysis demonstrates that FFR variability is predominantly driven by stenosis severity, which accounts for 85.4% of the total variance as a standalone main effect (S_1 = 0.854). In contrast, the presence of a pressure wire exerts a relatively limited direct influence, contributing only 7.6% to the variance (S_2 = 0.076). However, the analysis reveals a notable interaction effect (V_{12} 0.00136), which nearly doubles the wire's total impact to 14.6% (ST_2 = 0.146). This interaction highlights a critical physical phenomenon: the pressure wire's interference

with blood flow is not constant but is non-linearly amplified as the anatomical stenosis becomes more severe. Ultimately, while FFR remains primarily determined by anatomical severity, the wire-induced pressure drop represents a significant secondary factor that must be accounted for in severe lesions.