SUPPLEMETAL APPENDIX

SUPPLEMENTAL METHODS

Computational Fluid Dynamics (CFD)

In brief, the 3D anatomy of the artery was reconstructed from OCT images and biplane coronary angiography. The arterial lumen was reconstructed from digitized and segmented OCT frames using a specialized off-line workstation software, OPTIS ORW E.5.2 (Abbott Vascular, Inc, Temecula, CA). The methodology utilized to reconstruct the artery 3D centerline path from angiographic projections has previously been described in detailed.[1] The physical 3D path of the artery centerline was determined by using the corresponding traces of the geometric center of lumen from biplane angiographic projections. The lumen centroid from the segmented OCT images was sequentially stacked along the 3D lumen centroid derived from the angiographic projections to rebuild the 3D geometry of the artery. The 3D position of each OCT frame was determined from the reconstructed trajectory of lumen core and pullback speed. Proximal and distal anatomical landmarks were identified on both the OCT and the corresponding angiographic image, and the orientation of the side-branches were used to determine the absolute orientation of OCT geometry. The rotation of the frame was determined by using computational geometry and each frame was aligned perpendicular to the centerline. The boundary points of each frame were connected by spline curves to rebuild the luminal geometry in 3D space. A structured grid that used a body-fitted coordinate system was employed to represent the lumen volume. The lumen was divided into computational control volumes comprising 0.3-mm-thick slices along the segment, 40 equal intervals around the circumference (lumen interface), and 16 intervals in the radial direction from the center of the reconstructed lumen. Coronary blood flow for the arterial section being studied was measured by dividing true 3D volume of the segment calculated from the lumen borders, as described above, by the time required for the volume of blood contained within

the same section to be displaced by radio-opaque material during a contrast injection utilizing timing of cine frames. The region of interest was chosen free of significant side branches that may significantly alter the flow through the segment under investigation. Although it would have been desirable to incorporate the side branch blood flow into the CFD process, to avoid inaccuracies in the parent artery blood flow, and downstream inaccuracies of distal flow and distal ESS,[2] we were unable to perform CFD including the side branches since imaging of the side branches was not available for lumen segmentation in these datasets. We were therefore unable to quantify the blood flow diverted into the side branches by OCT.

The detailed intravascular flow characteristics were obtained by solving the transport equations governing the conservation of mass and momentum. We assumed that the arterial wall was stiff, and that blood was incompressible, homogeneous, steady flow, and Newtonian. The Newtonian viscosity is estimated based on average shear within the artery and hematocrit if it is available.[3] Unfortunately, we did not have individual hematocrit values available in the OPTICO-ACS data set, therefor we used a default value of 38.7% to adjust the viscosity in the Newtonian model. We have previously shown that using the average flow in steady-flow calculations yields essentially the same values of ESS (and related parameters) as calculating the average shear stress from the phasic solution.[4] The governing equations were integrated over the computational control volumes, and the resulting algebraic equations were solved by using a fully implicit, guess-and correct algorithm embedded in the PHOENICS computer code. The computations were considered converged when the maximum change in the velocity field between iterations was 0.1%. The inlet velocity was assumed to be uniform, developed flow was assumed to be established after an entrance length of 3mm, and flow was ignored for the first 3mm. The distortions introduced by these assumptions were insignificant at the Reynolds numbers observed in this study. This method of data acquisition and CFD analysis is highly reproducible.[1,3]

Gradients of shear stress on the lumen surface were calculated in the circumferential/axial upslope/downslope directions using first order divided difference. Shear stress gradient on the lumen wall, ESSG, is defined as the magnitude of the vector formed by the circumferential and the axial components of shear stress gradient. Each reconstructed coronary artery was divided along its entire length into 3-mm segments for characterization of vascular shear stress characteristics (Average ESS, Min ESS, Max ESS, Max ESSG, Max ESSG axial/circumferential/any directions). Min/Max ESS and ESSG for subsegments and plaques are determined from the averages of lowest and highest local ESS/ESSG values within 90° arcs around the circumference to minimize the expected noise amplification in gradient calculations. Within each plaque, ESSG upslope is defined separately as the maximum positive axial and circumferential component of ESSG, ESSG downslope is defined separately as the maximum of absolute values of negative axial and circumferential component ESSG (absolute value of minimum ESSG), and max ESSG any direction is the maximum magnitude of the gradient of ESS on the lumen surface.

Identification of Characteristics of Eroded Plaques

We determined the shape and nature of each eroded plaque utilizing OCT frames by scrolling up- and downstream along the long axis view and cross-sectional view of the OCT image. The plaque region of interest was standardized by marking:

(1) The proximal plaque shoulder (i.e., upslope) start frame, which was determined by identifying the start of intimal thickening and where the plaque starts to encroach into the lumen.

(2) The distal shoulder (i.e., downslope) end frame, where the plaque was no longer evident, and the vessel lumen was back to its reference configuration.

(3) The reference area was chosen in a normal, disease-free segment of the vessel located 5 mm proximal and distal to the shoulder regions of the plaque.

Each culprit plaque site was confirmed with the responsible core lab angiographer in the OPTICO-ACS study. The erosion pathology and thrombus were located within the plaque regions that were in proximity to a downslope or an upslope of the plaque, or in the middle of the plaque at the MLA.

Biosample collection and analysis

After diagnostic angiography and before PCI, systemic blood samples (SYS) were obtained by aspiration of 30 ml blood directly from the arterial sheath (right radial artery or femoral artery, **visual abstract**). Coronary thrombi and blood samples were obtained directly from the ACS-causing culprit lesion (CL) by aspiration of 30 ml blood using the Export Advance™ aspiration catheter system (Medtronic, Minneapolis, MN, USA, **visual abstract**). In order to prevent the blood from clotting all samples were obtained after heparin infusion. Blood samples were immediately processed. After filtering thrombotic components from the CL samples, flow cytometry-based immunophenotyping was performed as described below.

Flow cytometry-based immunophenotyping

Equal blood volume (30 ml) from all patients was withdrawn from the systemic arterial sheath (SYS) and local culprit lesion (CL). Immediately after withdrawal, whole EDTA-anticoagulated blood (100 µL) was incubated for 20 minutes with an antibody cocktail (anti-human CD14-Pacific Blue, CD16-BV510, CD4-BV605, CD45-BV711, CD3-AF488, CD26-PE, CD19-PE/Dazzle594, CD8–PE/Cy7, CD41–AF647M; all BioLegend, San Diego, USA), followed by a 1:10 dilution/fixation in 0.5% phosphate-buffered paraformaldehyde solution (final volume 1000 µL). Samples were stored in the dark at 4°C until data acquisition 16h to

24h later. Before data acquisition, samples were again diluted 1:10 in phosphate buffer and 1000 µL of the diluted samples (equals 10 µL of whole blood) were measured on an Attune NxT Acoustic Focusing Flow Cytometer. Events were acquired by triggering on $CD45^+$events with side scatter typical for lymphocytes and above. Kaluza v1.5 was used for data analysis.

Details on controls, antibodies, and gating procedure are provided below:

Antibody	Supplier	cat.no.	Laser	Detector
CD14-Pacific Blue	Biolegend	301828	violet (405 nm)	VL1 (440/50)
CD16-BV510	Biolegend	302048	violet (405 nm)	VL2 (512/25)
CD4-BV605	Biolegend	317438	violet (405 nm)	VL3 (603/48)
CD45-BV711	BioLegend	304050	violet (405 nm)	VL4 (710/50)
CD3-AF488	Biolegend	300320	blue (488 nm)	BL1 (530/30)
CD26-PE	Miltenyi	130-093-440	blue (488 nm)	BL2 (574/26)
CD19-PE/Dazzle594	Biolegend	302252	blue (488 nm)	BL3 (695/40)
CD8–PE/Cy7	Biolegend	300914	blue (488 nm)	BL4 (780/60)
CD41–AF647	Biolegend	303726	red (638 nm)	RL1 (670/14)

Gating procedure

Compensated data were first used for duplet exclusion based on FSC-H/FCS-W and $CD45^+$selection (leukocytes), followed by separation of $CD3^+$ $CD14^-$ and $CD14^+CD3^-$ events. Each population was then carefully selected based on typical forward/side scatter characteristics. Monocyte subtypes were then identified based on their CD14/CD16 expression and T cells were sub-divided into $CD4^+$ and $CD8^+$ T cells. B cells were identified from $CD45^+$ singlets based on their low side scatter and CD19 positivity. Neutrophils were defined as high side scatter $CD45^+$ singlets with CD16 positivity and CD14 negativity. To

identify NK cells, $CD16^+$ events with low side scatter were first selected from $CD45^+$ singlets. $CD14^-$ $CD3^-$ events were defined as NK cells. Monocyte-platelet-, T-cell-platelet- and neutrophil-platelet-aggregates were defined as before, followed by selection of $CD41^+$ events from each specific cell type.

Plasma cytokine profiling

Concentrations of interleukin (IL)-1 β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, basic fibroblast growth factor (bFGF), granulocyte-macrophage colony-derived factor (GM-CSF), interferon (IFN)-gamma, interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1 alpha, regulated on activation, normal T cell expressed and secreted (RANTES), soluble CD40 ligand, tumor necrosis factor (TNF)-alpha, vascular endothelial growth factor (VEGF), and transforming growth factor (TGF)-β were assessed in platelet-poor anticoagulated plasma samples by cytokine bead arrays (CBA single plex, BD) according to the manufacturer´s instructions. Concentrations of IL-17A, granzyme A, perforin and granulysin were assessed in platelet-poor anticoagulated plasma samples by LegendPlex bead array (BioLegend) according to the manufacturer´s protocol. Neutrophil gelatinase-associated lipocalin (NGAL; BioPorto) and MIP-1β (R&D Systems) were assessed in platelet-poor anticoagulated plasma samples by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer´s instructions.

Matrix Metalloproteinase (MMP) Activity in Supernatants and Plasma Samples from Isolated PMNs: Isolated PMNs were either activated by a human recombinant TLR2/1 agonist (Pam3CSK4, Invivogen, USA) at a final concentration of 500ng/ml for a total time of 120 minutes or pre-treated with a selective inhibitory anti-TLR2 antibody (mouse monoclonal IgG1 anti-human antibody to TLR2 (clone T2.5, Cat. Number ab16894, abcam,

Cambridge, England) at a final concentration of 1.25µg/ml for 15min prior to exposure to Pam3CSK4 as described above. Fluorescence gelatine zymography was performed according to the manufacturer's instructions (Invitrogen, Fisher Scientific, Göteborg, Sweden) to quantify gelatinase activity of the pre-treated PMNs in a time course. Furthermore, using the same method the gelatinolytic activity in local and systemic citrate-plasma samples was also assessed. Gelatine gel zymography of the above-described supernatants was used for size discrimination between pro-MMP2/MMP2 (80/72kDa), pro-MMP9/MMP9 (92/84kDa) and MMP9/Neutrophil Gelatinase Associated Lipocalin (NGAL) complex (125kDa) and performed as previously described.[5]

Immunoenzymatic Assay for Detection of MMP9, NGAL and Hyaluronan Plasma Concentration: The concentration of MMP9, neutrophil-gelatinase associated lipocalin (NGAL) and hyaluronan (HA) in human plasma samples were assessed by commercially available ELISA kits (MMP 9 Human ELISA, Thermo Fischer, USA; NGAL ELISA Kit from Bioporto, Hamburg; and Hyaluronic Acid (HA) Test Kit, Corgenix, Broomfield, CO, USA, respectively). All tests were performed according to the manufacturer's instructions.

SUPPLEMENTAL TABLES

Supplemental Table 1: Baseline Characteristics of the Study Population (n=32)	
Patient Characteristics	
Age, years	63.0 ± 10
Male, n (%)	27 (84%)
Family history for CAD, n (%)	14 (44%)
Smoking, n (%)	7 (22%)
Diabetes mellitus, n (%)	7 (22%)
Arterial hypertension, n (%)	23 (72%)
Dyslipidemia, n (%)	17 (53%)
BMI, mean ± SD	27.5 ± 4
Previous history of PCI, n (%)	2 (6%)
Laboratory Data	
Total cholesterol, mg/dL	172 ± 42
LDL cholesterol, mg/dL	112 ± 40
Serum creatinine, mg/dL	1.00 ± 0.2
Hemoglobin, g/dL	14.4 ± 2.0
Leukocytes, per nL	11.2 ± 4.1
Lymphocytes, per nL	2.3 ± 0.7
hs-CRP, mg/L	6.4 ± 20.3
ACS Characteristics	
Presentation as STE-ACS, n (%)	23 (72%)
CK peak (U/I), mean ± SD	1259 ± 1441
LV-EF at discharge (%), mean ± SD	54 ± 11

Values are represented as mean ± SD and numbers (n) and percentage (%).

BMI = body mass index, CK = creatine kinase, hs-CRP = high sensitivity C-reactive protein, LDL = low density lipoprotein, LV-EF = left ventricular ejection fraction, PCI = percutaneous coronary intervention, STE-ACS = ST elevated - acute coronary syndrome.

Supplemental Table 2: Categorical Variables Tertiles of Culprit Lesion and Culprit Lesion Ratios of Immune Cells (n = 32)			
Immune Cells	**Culprit Lesion** Median (IQR)	**Systemic** Median (IQR)	**Culprit Lesion Ratio** Median (IQR)
T-lymphocytes abs	[1] **1408** (787–1978)	[1] **1186** (668–1650)	[1] **0.90** (0.81–0.93)
	[2] **3509** (3136–3997)	[2] **3596** (2643–4284)	[2] **1.01** (0.97–1.05)
	[3] **7219** (5292–9323)	[3] **7584** (5778–10362)	[3] **1.24** (1.15–1.36)
CD4+ T-lymphocytes abs	[1] **738** (404–1403)	[1] **659** (336–1336)	[1] **0.88** (0.77–0.95)
	[2] **1880** (1823–2609)	[2] **2113** (1789–2621)	[2] **1.03** (0.99–1.05)
	[3] **4654** (3617–6861)	[3] **4520** (3910–7684)	[3] **1.23** (1.10–1.46)
CD8+ T-lymphocytes abs	[1] **274** (101–502)	[1] **224** (97–421)	[1] **0.86** (0.76–0.87)
	[2] **838** (743–2938)	[2] **847** (712–1462)	[2] **0.99** (0.95–1.04)
	[3] **2013** (1524–2938)	[3] **2101** (1699–2881)	[3] **1.25** (1.18–1.41)
NKT-cells abs	[1] **11** (4–24)	[1] **8** (4–22)	[1] **0.76** (0.71–0.83)
	[2] **45** (35–48)	[2] **45** (35–52)	[2] **0.94** (0.91–1.02)
	[3] **80** (65–124)	[3] **87** (66–121)	[3] **1.49** (1.28–1.88)
B-cells abs	[1] **328** (183–547)	[1] **265** (192–588)	[1] **0.79** (0.73–0.85)
	[2] **1088** (1011–1310)	[2] **1308** (965–1428)	[2] **0.95** (0.93–1.01)
	[3] **2220** (1604–3980)	[3] **2275** (1770–5021)	[3] **1.17** (1.07–1.24)
Total monocytes abs	[1] **1536** (1271–1743)	[1] **1577** (1284–1749)	[1] **0.75** (0.70–0.86)
	[2] **2265** (2205–2609)	[2] **2323** (2223–2687)	[2] **0.96** (0.90–0.99)
	[3] **4270** (3382–6785)	[3] **4846** (3957–7812)	[3] **1.09** (1.06–1.26)
Classical monocytes abs	[1] **1400** (1190–1584)	[1] **1430** (1212–1678)	[1] **0.76** (0.68–0.85)
	[2] **2180** (2100–2504)	[2] **2186** (2130–2514)	[2] **0.95** (0.90–1.00)
	[3] **3946** (3213–5755)	[3] **4638** (3589–7079)	[3] **1.09** (1.04–1.26)
Intermediate monocytes abs	[1] **18** (12–22)	[1] **17** (10–27)	[1] **0.58** (0.33–0.82)
	[2] **41** (37–49)	[2] **45** (39–50)	[2] **1.11** (0.99–1.21)
	[3] **112** (68–174)	[3] **99** (70–164)	[3] **1.49** (1.33–1.67)
Alternative monocytes abs	[1] **30** (17–43)	[1] **35** (13–49)	[1] **0.76** (0.51–0.83)
	[2] **63** (54–78)	[2] **82** (66–97)	[2] **0.97** (0.92–1.04)
	[3] **147** (136–255)	[3] **147** (131–241)	[3] **1.30** (1.22–1.69)
Granulocytes abs	[1] **23502** (13446–28506)	[1] **24305** (18564–35685)	[1] **0.74** (0.67–0.79)
	[2] **40496** (32982–50804)	[2] **44775** (38439–59531)	[2] **0.89** (0.84–0.92)
	[3] **67030** (59475–72196)	[3] **74878** (66811–88651)	[3] **1.03** (1.00–1.05)
Neutrophils abs	[1] **20073** (10463–25855)	[1] **20073** (10463–25855)	[1] **0.74** (0.59–0.78)
	[2] **35052** (31039–40998)	[2] **37386** (34695–48149)	[2] **0.89** (0.84–0.92)
	[3] **63302** (52782–67061)	[3] **70172** (59969–81817)	[3] **1.03** (1.01–1.07)
NK-cells abs	[1] **695** (411–905)	[1] **691** (242–860)	[1] **0.79** (0.67–0.83)
	[2] **1314** (1066–1768)	[2] **1395** (1138–2158)	[2] **0.97** (0.88–1.01)
	[3] **3053** (2630–4108)	[3] **3603** (2932–3988)	[3] **1.26** (1.12–1.39)

Values are represented as median and interquartile range (IQR; 25^{th}-75^{th} percentile) of absolute cell count of immune cells. Tertiles low [1] – high [3]. Unit of measurement is absolute cell count [abs]/10µl of whole blood. Culprit lesion ratio (local level culprit lesion site/ systemic level arterial sheath).

NK-cells = natural killer cells, NKT-cells = natural killer T-cells, T-cells = T-lymphocytes.

Supplemental Table 3: Categorical Variables Tertiles of Culprit Lesion and Culprit Lesion Ratios of Cytokines and Chemokines (n = 32)			
Cytokines and Chemokines	**Culprit Lesion** Median (IQR)	**Systemic** Median (IQR)	**Culprit Lesion Ratio** Median (IQR)
IL1-β pg/mL	[1] **5.08** (3.19–6.43)	[1] **5.02** (3.50–6.72)	[1] **0.67** (0.47–0.77)
	[2] **10.34** (8.67–12.74)	[2] **11.42** (8.31–12.18)	[2] **1.00** (0.88–1.05)
	[3] **21.81** (17.65–47.09)	[3] **17.56** (16.66–49.99)	[3] **1.63** (1.40–2.00)
IL-2 pg/mL	[1] NA	[1] NA	[1] **0.9** (0.89–0.96)
	[2] **11.20** (11.20–11.20)	[2] **11.20 (**11.20–11.20)	[2] **1.00** (1.00–1.00)
	[3] **14.35** (12.14–19.21)	[3] **12.60** (12.44–15.86)	[3] **1.21** (1.13–1.28)
IL-3 pg/mL	[1] **1.73** (1.67–1.86)	[1**] 1.47** (0.59–1.86)	[1] **0.43** (0.39–0.6)
	[2] **2.50** (2.17–2.90)	[2] **3.25** (2.12–4.11)	[2] **0.79** (0.69–0.92)
	[3] **5.73** (3.50–14.23)	[3**] 6.09** (5.27–12.15)	[3] **1.63** (1.26–6.31)
IL-4 pg/mL	[1] NA	[1] NA	[1] **0.77** (0.62–0.79)
	[2] **1.40** (1.40–1.40)	[2] **1.40** (1.40–1.40)	[2] **1.00** (1.00–1.00)
	[3] **2.22** (1.66–2.72)	[3] **2.02** (1.56–3.26)	[3] **1.30** (1.14–1.74)
IL-5 pg/mL	[1] NA	[1] NA	[1] NA
	[2] **1.10** (1.10–1.10)	[2] **1.10** (1.10–1.10)	[2] **1.00** (1.00–1.00)
	[3] NA	[3] NA	[3] NA
IL-6 pg/mL	[1] **5.84** (1.6–5.88)	[1] **3.89** (1.60–5.22)	[1] **0.63** (0.60–0.67)
	[2] **8.81** (6.31–10.49)	[2] **6.12** (5.42–9.06)	[2] **0.99** (0.93–1.09)
	[3] **13.05** (12.38–17.41)	[3] **14.86** (13.86–18.71)	[3] **1.80** (1.40–2.42)
IL-8 pg/mL	[1] **4.54** (2.44–6.96)	[1] **3.59** (2.85–4.40)	[1] **1.01** (0.67–1.07)
	[2] **8.82** (8.01–10.55)	[2] **7.01** (6.57–7.88)	[2] **1.2** (1.15–1.31)
	[3] **14.37** (12.07–23.95)	[3] **11.91** (10.10–14.31)	[3] **1.76** (1.66–2.78)
IL-10 pg/mL	[1] **1.99** (1.68–2.33)	[1] **1.69** (1.52–1.94)	[1] **0.93** (0.81–1.00)
	[2] **3.16** (2.58–3.60)	[2] **2.59** (2.46–2.88)	[2] **1.14** (1.05–1.25)
	[3] **9.49** (4.40–16.60)	[3] **5.94** (3.42–17.4)	[3] **1.45** (1.41–2.07)
IL-13 pg/mL	[1] **3.28** (3.04–3.79)	[1] **2.87** (2.47–3.09)	[1] **0.87** (0.81–0.91)
	[2] **4.70** (4.38–4.89)	[2] **4.58** (3.95–4.93)	[2] **1.00** (1.00–1.00)
	[3] **6.18** (5.43–7.81)	[3] **6.87** (5.43–9.71)	[3] **1.33** (1.22–1.52)
IL-17 pg/mL	[1] **14.36** (13,64–14.77)	[1] **10.27** (9.41–12.83)	[1] **0.9** (0.69–0.93)
	[2] **17.96** (15.66–18.48)	[2] **14.36** (13.14–15.63)	[2] **1.16** (1.11–1.23)
	[3] **24.11** (19.79–41.76)	[3] **26.15** (19.1–36.58)	[3] **1.44** (1.39–1.74)
GM-CSF pg/mL	[1] **1.99** (1.73–2.09)	[1] **2.00** (1.83–2.22)	[1] **0.75** (0.73–0.81)
	[2] **2.67** (2.34–3.00)	[2] **2.50** (2.38–2.74)	[2] **1.15** (0.95–1.20)
	[3] **3.24** (3.10–6.99)	[3] **2.85** (2.81–5.21)	[3] **1.31** (1.24–1.49)
INF-γ pg/mL	[1] **8.78** (7.85–10.35)	[1] **7.86** (5.60–8.79)	[1] **1.00** (0.94–1.02)
	[2] **12.45** (11.24–13.25)	[2] **10.95** (10.19–11.68)	[2] **1.14** (1.11–1.2)
	[3] **16.77** (15.47–22.16)	[3] **15.79** (13.28–17.66)	[3] **1.47** (1.29–1.75)
IP-10 pg/mL	[1] **262.80** (192.1–323.4)	[1] **196** (169.5–225.9)	[1] **0.93** (0.60–1.04)
	[2] **435.7** (405.3–495.9)	[2] **317.1** (258.4–356.6)	[2] **1.32** (1.20–1.44)
	[3] **630.3** (558.10–1083)	[3] **592.1** (511.1–954)	[3] **1.81** (1.59–1.98)
MCP-1 pg/mL	[1] **30.37** (20.18–36.47)	[1] **32.8** (27.26–35.52)	[1] **0.55** (0.39–0.58)
	[2] **55.85** (44.15–72.21)	[2] **64.38** (54.16–82.36)	[2] **0.90** (0.80–0.93)
	[3] **122.6** (86.38–131.9)	[3] **142.5** (126.2–211.3)	[3**] 1.19** (1.13–1.33)
MIP-1 α pg/mL	[1] **0.82** (0.61–1.78)	[1] **1.12** (0.20–1.25)	[1] **0.65** (0.35–1.11)
	[2] **2.16** (1.91–2.69)	[2] **1.56** (1.49–1.65)	[2] **1.45** (1.21–1.77)
	[3] **4.62** (3.17–17.74)	[3] **2.21** (1.74–5.32)	[3] **2.12** (2.03–8.51)
MIP-1 β pg/mL	[1] **7.61** (5.57–9.79)	[1] **9.45** (8.70–10.62)	[1] **0.57** (0.34–0.69)
	[2] **13.93** (12.16–17.22)	[2] **17.68** (15.17–19.84)	[2] **0.85** (0.74–0.88)
	[3] **28.84** (21.83–35.40)	[3] **25.51** (24.40–38.20)	[3] **1.13** (1.04–1.62)
RANTES pg/mL	[1] **1319** (1259–1366)	[1] **1567** (1336–1840)	[1] **0.66** (0.62–0.84)
	[2] **2684** (1857–2857)	[2] **1950** (1874–2013)	[2] **1.19** (1.09–1.24)
	[3] **3184** (3011–3380)	[3] **2447** (2239–2791)	[3] **1.50** (1.44–1.72)
CD40 ligand pg/mL	[1] **41.40** (29.86–103.9)	[1] **104.9** (25.94–118.4)	[1] **0.57** (0.25–0.59)
	[2] **153.6** (113.5–199)	[2] **159.6** (139–178.2)	[2] **0.80** (0.70–1.00)

	[3] **249.5** (214–495)	[3] **284** (250.2–332.8)	[3] **1.64** (1.58–2.07)
TNF-α pg/mL	[1] **2.61** (1.78–3.37)	[1] **3.04** (2.50–3.83)	[1] **0.48** (0.32–0.83)
	[2] **4.92** (4.89–5.23)	[2] **4.92** (4.80–5.57)	[2] **1.01** (1.00–1.05)
	[3] **9.94** (7.66–41.02)	[3] **8.84** (8.04–45.85)	[3] **1.42** (1.23–1.89)
VEGF pg/mL	[1] **4.50** (4.50–4.50)	[1] **4.50** (4.50–4.50)	[1] **0.68** (0.63–0.92)
	[2] **6.77** (6.72–7.11)	[2] **6.20** (6.13–6.58)	[2] **1.00** (1.08–1.18)
	[3] **11.15** (8.40–33.01)	[3] **10.37** (6.78–27.28)	[3] **1.50** (1.31–1.57)
TGF-β ng/mL	[1] NA	[1] NA	[1] NA
	[2] **14.90** (14.90–14.90)	[2] **14.90** (14.90–14.90)	[2] **1.00** (1.00–1.00)
	[3] NA	[3] NA	[3] NA
bFGF pg/mL	[1] **16.86** (14.51–22.76)	[1] **18.34** (16.68–22.27)	[1] **0.79** (0.76–0.83)
	[2] **28.61** (26.67–31.96)	[2] **29.86** (26.67–36.22)	[2] **0.98** (0.91–1.00)
	[3] **38.62** (36.84–42.17)	[3] **42.17** (40.14–45.10)	[3] **1.14** (1.07–1.2)
Granzyme A pg/mL	[1] **7.78** (5.90–8.30)	[1] **5.28** (5.24–5.77)	[1] **0.94** (0.76–0.98)
	[2] **10.30** (9.46–11.35)	[2] **7.51** (7.10–8.34)	[2] **1.141** (1.22–1.47)
	[3] **17.10** (12.90–39.51)	[3] **11.76** (9.03–21.15)	[3] **2.02** (1.73–2.68)
Perforin pg/mL	[1] **802.8** (749.9–894.1)	[1] **19.44** (18.21–71.14)	[1] **0.65** (0.39–0.84)
	[2] **1902** (1805–1983)	[2] **1378** (425–2147)	[2] **1.63** (1.34–2.01)
	[3] **4581** (2959–12219)	[3] **3330** (2479–4413)	[3] **45.21** (18.23–56.34)
Granulysin pg/mL	[1] **831.7** (626.6–1043)	[1] **201.9** (185.8–261.3)	[1] **0.75** (0.59–0.87)
	[2] **5564** (2312–6821)	[2] **3150** (1751–5899)	[2] **1.59** (1.07–2.34)
	[3] **15702** (13430–43701)	[3] **10184** (8002–48575)	[3] **4.06** (3.53–4.88)
NGAL ng/mL	[1] **309.7** (209.3–362.2)	[1] **340.3** (293.7–453.1)	[1] **0.68** (0.61–0.71)
	[2] **591.1** (495.1–610.5)	[2] **745.6** (593.3–806.3)	[2] **0.79** (0.75–0.87)
	[3] **911.8** (652.4–1031)	[3] **1050** (949.7–1228)	[3] **0.95** (0.92–0.98)
Hyaluronic acid ng/mL	[1] **25.85** (15.86–30.26)	[1] **28.05** (18.73–50.97)	[1] **0.4** (0.30–0.56)
	[2] **70.31** (44.08–80.03)	[2] **84.71** (71.43–114.1)	[2] **0.79** (0.71–0.84)
	[3] **206.3** (181–530.3)	[3] **260.8** (231.8–1080)	[3] **1.07** (0.94–1.46)
MMP-9 ng/mL	[1] **30.82** (19.60–45.81)	[1] **41.96** (36.31–55.38)	[1] **0.55** (0.39–0.67)
	[2] **70.63** (60.87–88.48)	[2] **81.93** (72.76–101.0)	[2] **0.93** (0.74–1.03)
	[3] **154.9** (126.9–269.9)	[3] **134.1** (121.0–168.2)	[3] **1.66** (1.29–2.64)
MMP-9 activity u/µL	[1] **0.07** (0.07–0.08)	[1] **0.07** (0.07–0.08)	[1] **0.98** (0.88–0.98)
	[2] **0.08** (0.08–0.39)	[2] **0.08** (0.08–0.37)	[2] **1.03** (1.03–1.06)
	[3] **0.55** (0.46–0.61)	[3] **0.44** (0.40–0.50)	[3] **1.35** (1.13–1.50)

Values are represented as median and interquartile range (IQR; 25^{th}-75^{th} percentile) of cytokines and chemokines. Tertiles low [1] – high [3]. Unit of measurements (plasma concentration: pg/mL, ng/mL, u/µL). Culprit lesion ratio (local level culprit lesion site/systemic level arterial sheath).

bFGF = basic fibroblast growth factor, GM-CSF = granulocyte-macrophage colony-stimulating factor, IL = interleukin, INF-γ = interferon-γ, IP-10 = interferon-gamma inducible Protein, MCP-1 = monocyte chemoattractant protein-1, MIP-1 α = macrophage inflammatory protein-1 α, MIP-1 β = macrophage inflammatory protein-1 β, MMP-9 = matrix metallopeptidase-9, NGAL = neutrophil gelatinase-associated lipocalin, NK-cells = natural killer cells, NKT-cells = natural killer T-cells, RANTES = Regulated on Activation Normal

T-lymphocytes Expressed and Secreted, T-cells = T-lymphocytes, TGF-β = transforming growth factor –β, TNF- α = tumor necrosis factor- α, VEGF = vascular endothelial growth factor.

Supplemental Table 4. Shear Stress Metrics/Anatomical Metrics and Their Association to Inflammatory Mediators	
A. Inflammatory Markers Associated with ESS Metrics/Anatomical Metrics	**B. Inflammatory Markers Not Associated with ESS Metrics/Anatomical Metrics**
Inflammatory cells	**Inflammatory cells**
T-lymphocytes CD4+ T-lymphocytes CD8+ T-lymphocytes NKT-cells Intermediate monocytes Neutrophils NK-cells	B-cells Total monocytes Classical monocytes Alternative monocytes Granulocytes
Cytokines and Chemokines	**Cytokines and Chemokines**
IL1-β IL-2 IL-3 IL-4 IL-6 MIP-1 β Hyaluronic acid Perforin Granulysin bFGF	IL-5 IL-8 IL-10 IL-13 IL-17 GM-CSF INF-γ IP-10 MCP-1 MIP-1 α RANTES CD40 ligand TNF-α VEGF TGF-β Granzyme A NGAL MMP-9 MMP-9 activity

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