6th Annual COVADIS Summit

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Inflammation in vasospastic angina

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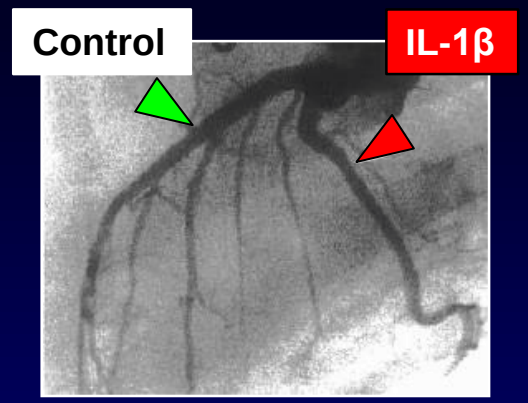
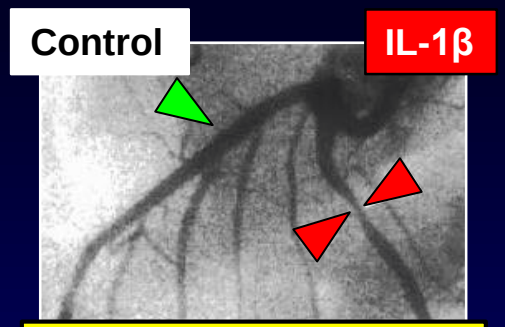
Background (1) Involvement of adventitial inflammation and Rho-kinase activation in coronary spasm

Porcine spasm model

Baseline

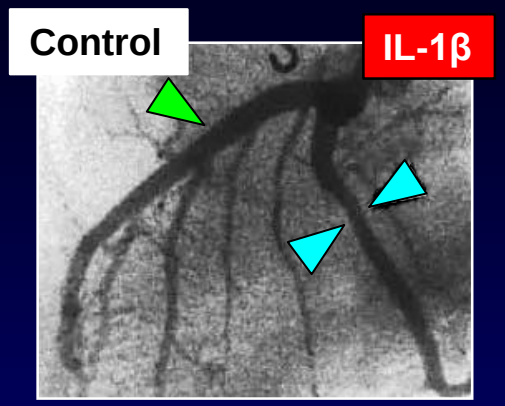


Serotonin (5-HT)

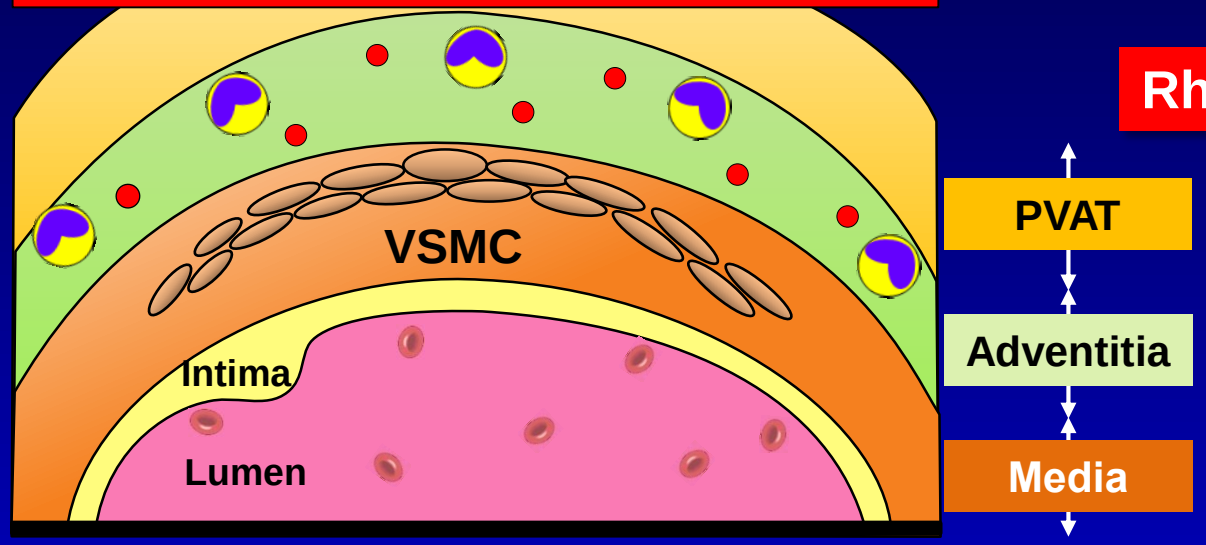


Coronary spasm

5-HT after Rho-kinase inhibition



Application of IL-1β to adventitia



Adventitial inflammation

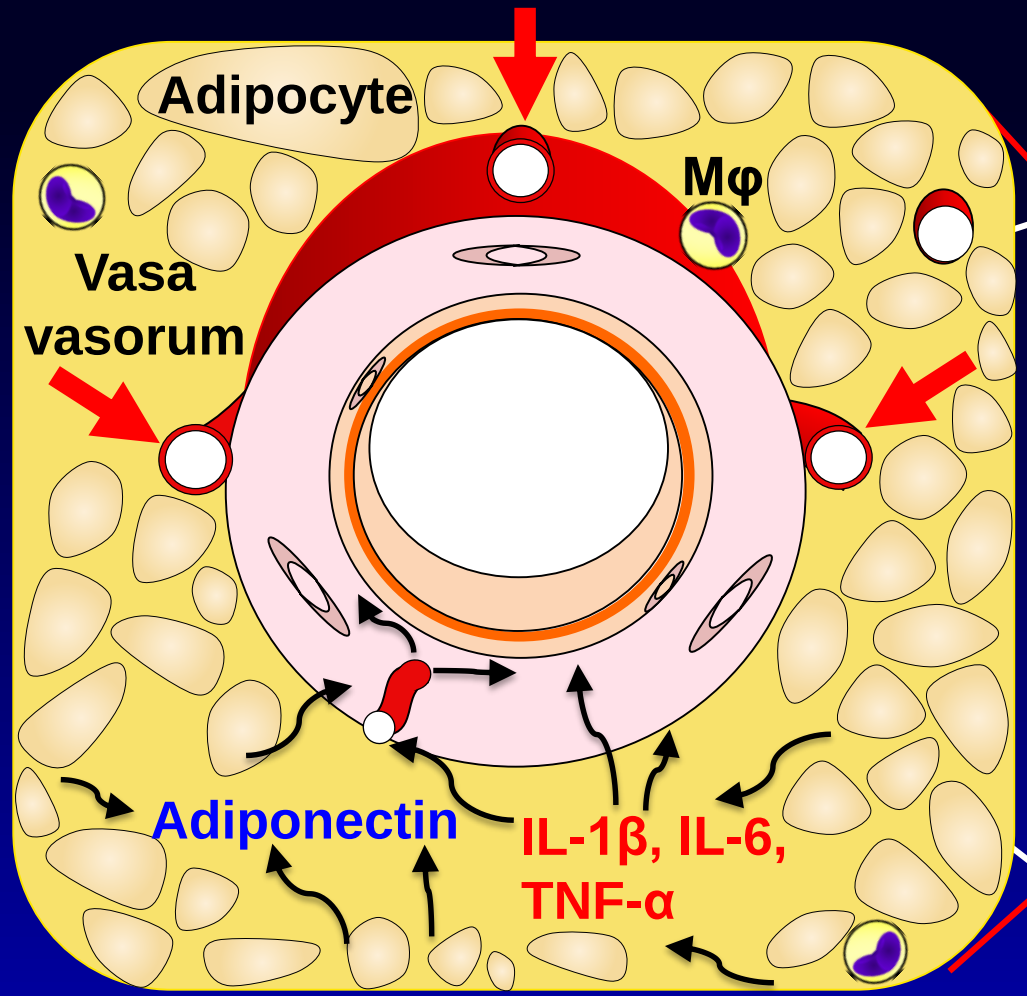
Rho-kinase activation ⊖ Rho-kinase inhibitors

VSMC hypercontraction

Coronary spasm

(Shimokawa H. Williams Harvey Lecture. *Eur Heart J* 2014.)

Background (2) Important roles of coronary adventitia and perivascular adipose tissue in cardiovascular disease

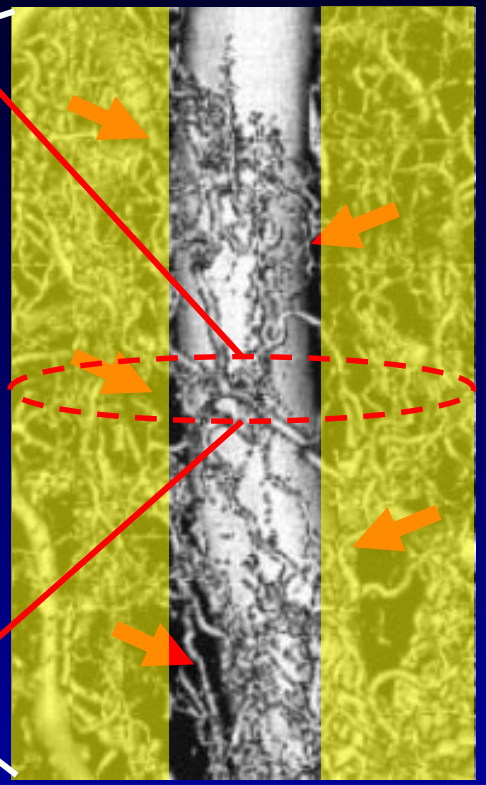


(Mahabadi AA, et al. *Eur Heart J* 2009.)

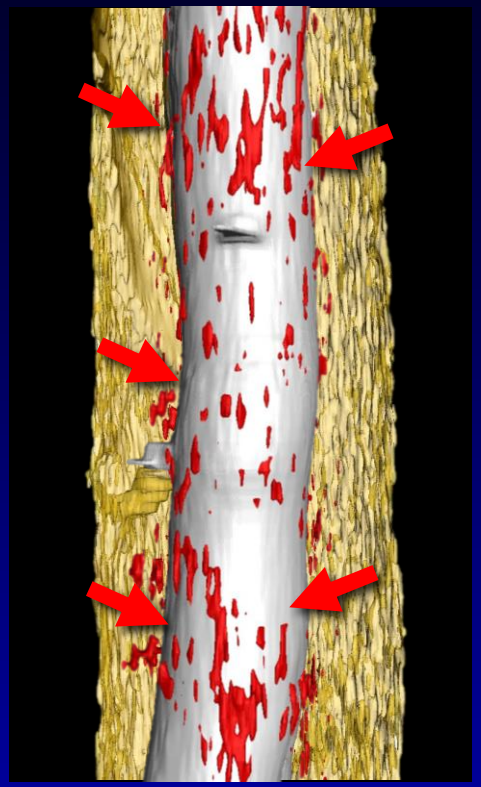
(Ohyama K, Shimokawa H, et al. *Circ J* 2016.)

Perivascular components

- Adventitial vasa vasorum (VV)
- Perivascular adipose tissue (PVAT)



Micro CT

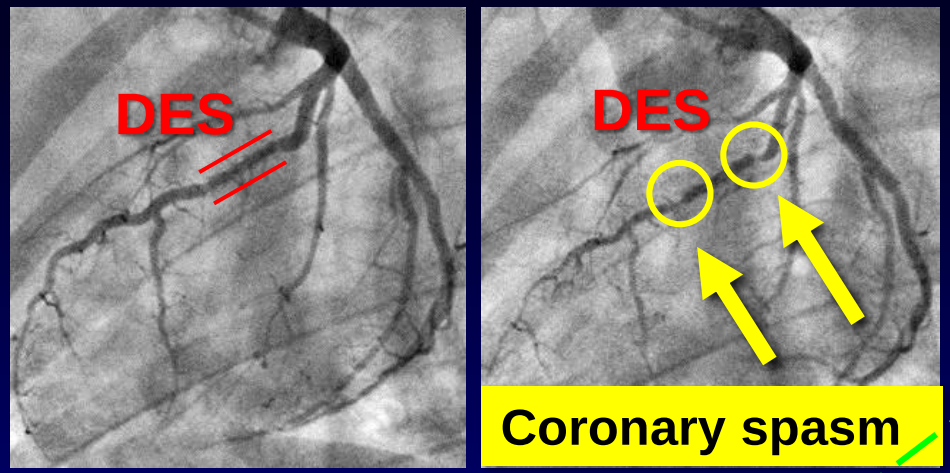


3D-OCT

(Nishimiya K, Shimokawa H, et al. *Circ J* 2014.)

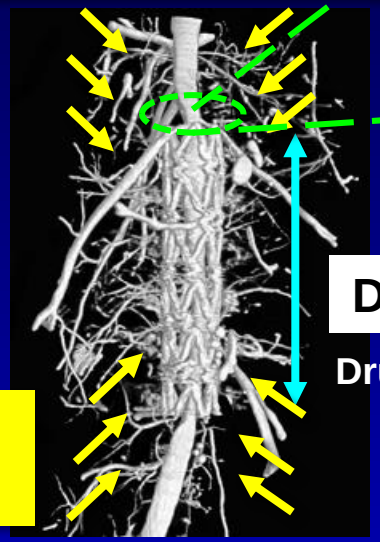
Background (3) Enhanced adventitial VV formation and histological validation with OCT in coronary spasm

DES-induced coronary spasm (pigs)



Coronary spasm

3D micro CT



DES

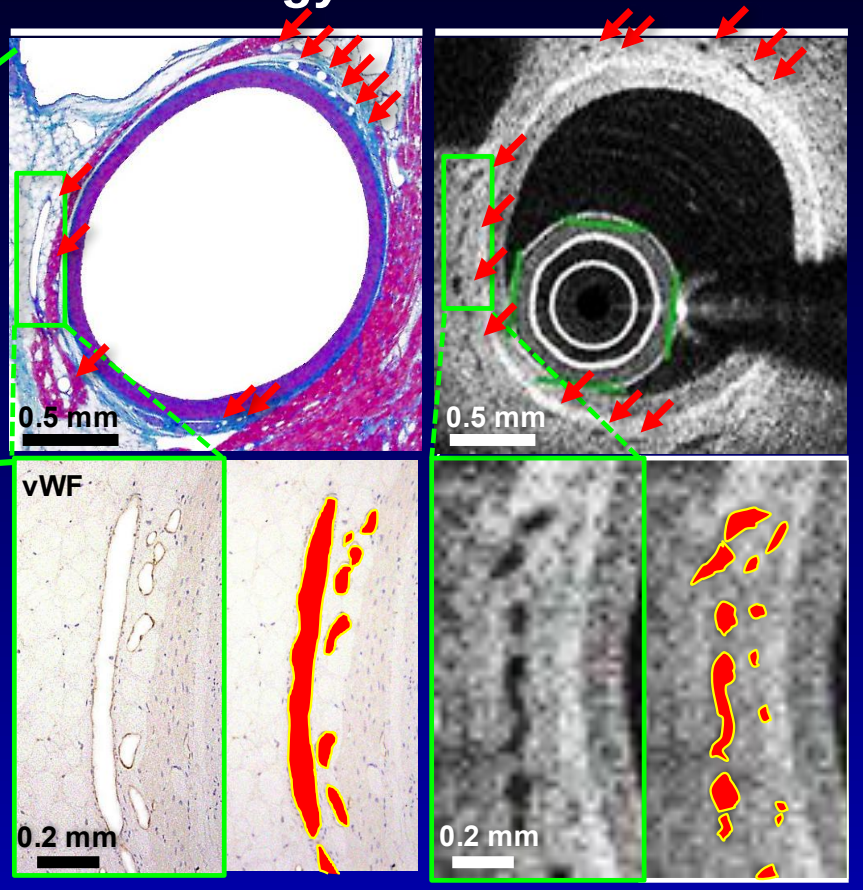
Drug-eluting stents

Enhanced adventitial VV formation

(Nishimiya K, Shimokawa H, et al. *Circ J* 2015.)

Histological validation for OCT measurement of adventitial VV

Histology OCT



(Nishimiya K, Shimokawa H, et al. *Circ J* 2015.)

Experimental study

Importance of inflammatory changes of perivascular adipose tissue in the pathogenesis of DES-induced hyperconstricting responses in pigs in vivo

(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

Methods: Study protocol

Animals: 10 domestic male pigs

Stent implantation

Everolimus eluting stent (EES) ⇒ either LAD or LCX
Control ⇒ non-stented coronary artery

Follow-up coronary angiography (1 month)

Coronary vasoconstricting responses
- Serotonin before and after hydroxyfasudil

Coronary vasodilating responses
- Nitroglycerin
- Bradykinin before and after N^G-monomethyl-L-arginine (L-NMMA)

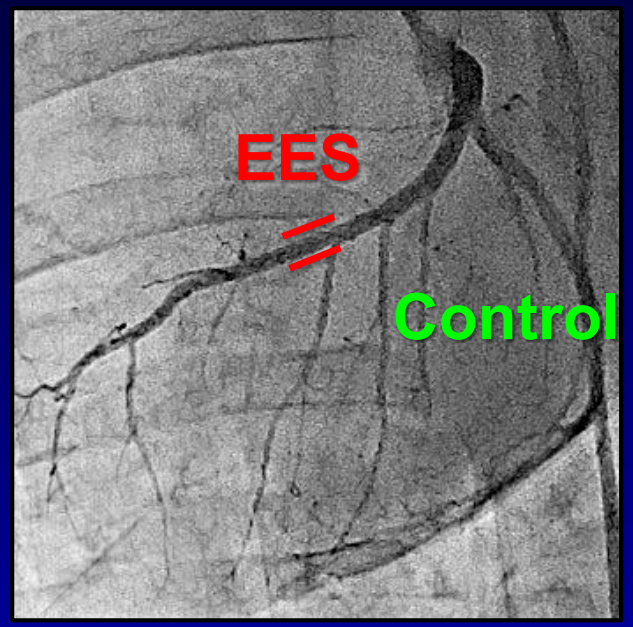
Sacrifice (1 month)

- PVAT imaging: ex-vivo ^{18}F-FDG PET/CT, autoradiography
- Histology
- RT-PCR

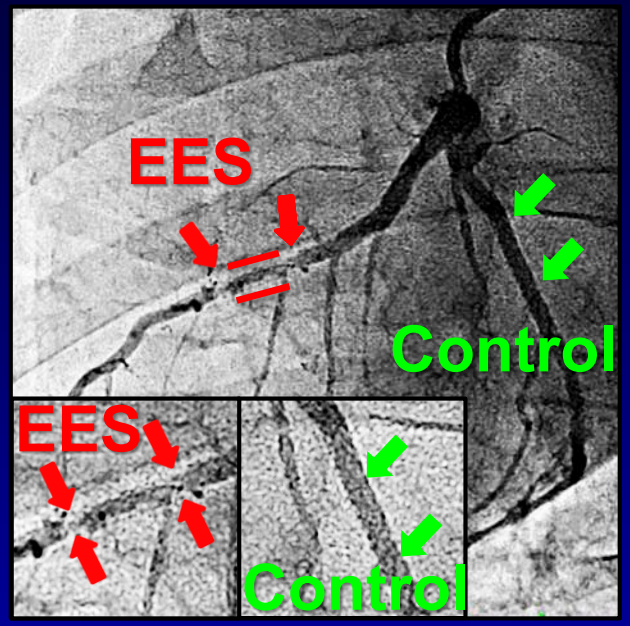
(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

Results (1) Enhanced coronary vasoconstrictions at EES edges compared with control sites

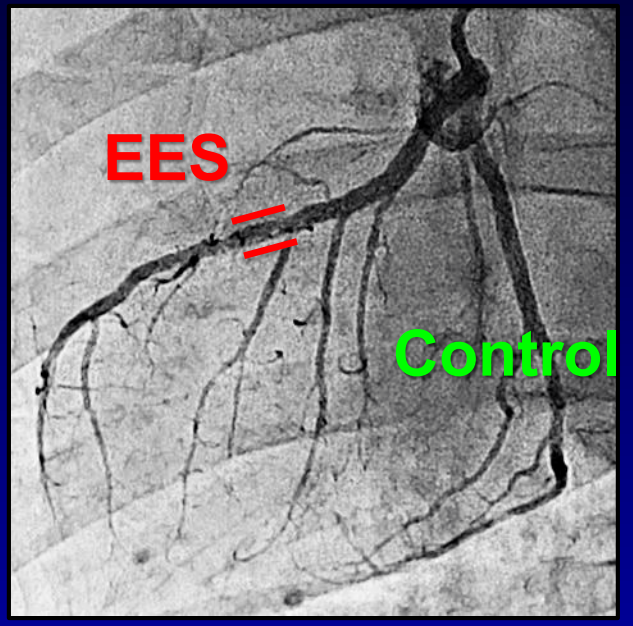
Nitroglycerin



Serotonin



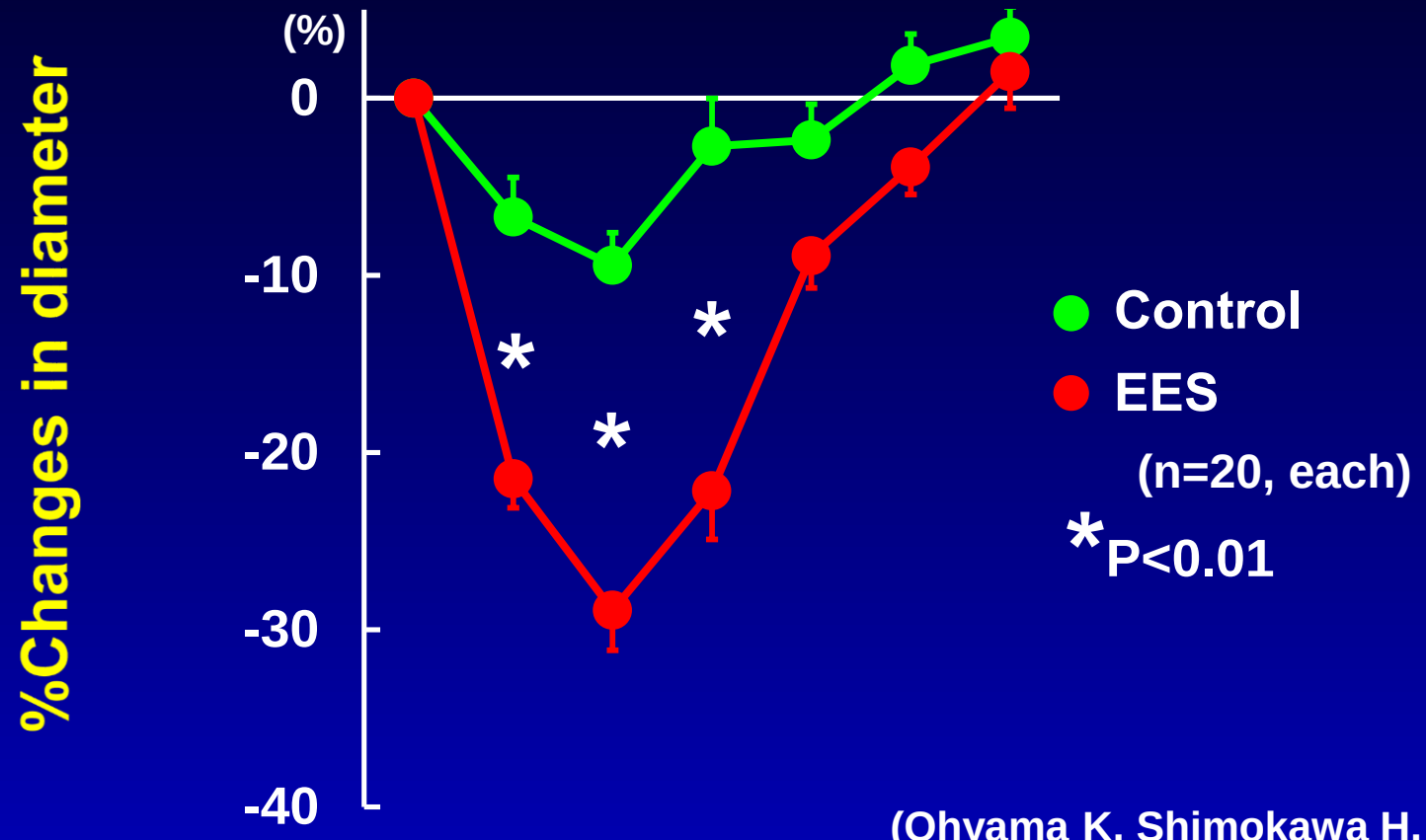
Serotonin after hydroxyfasudil



(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

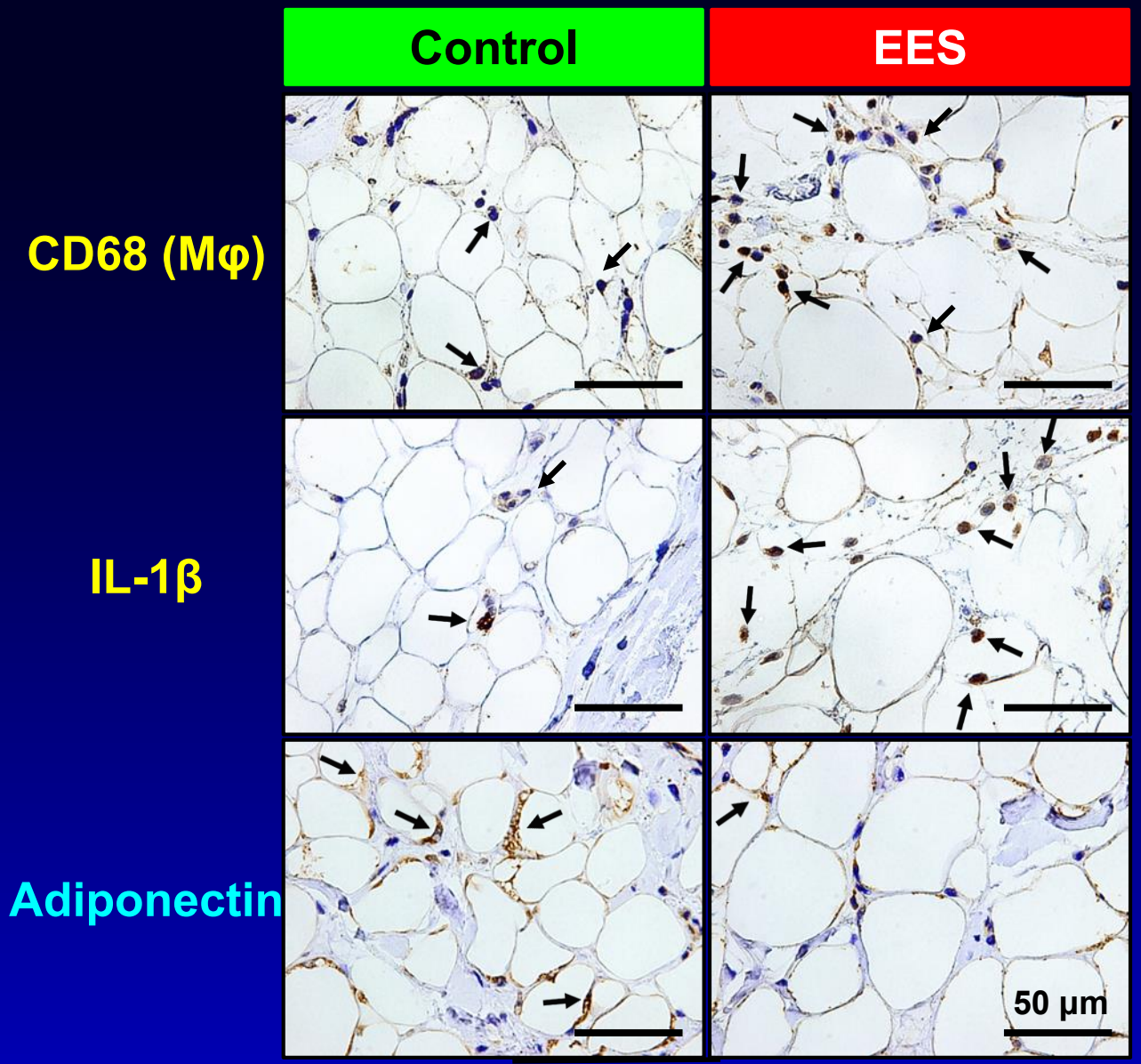
Results (2) Enhanced coronary vasoconstrictions at EES edges compared with control sites

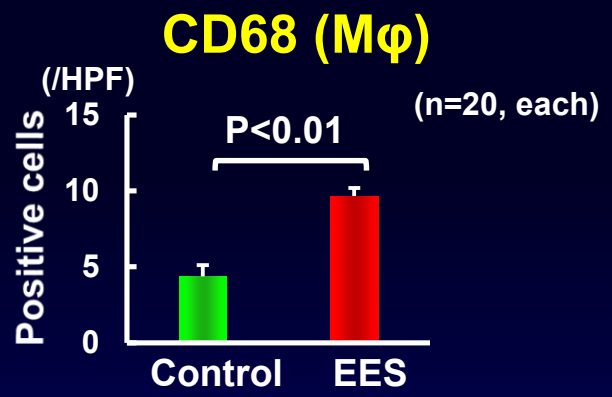
Hydroxyfasudil	—	—	—	90	300	90	300	(μg/kg)
Serotonin	—	10	100	100	100	—	—	(μg/kg)

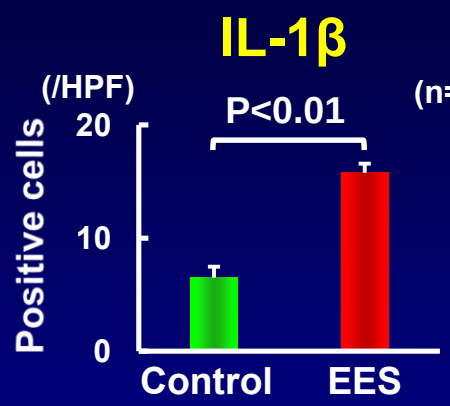


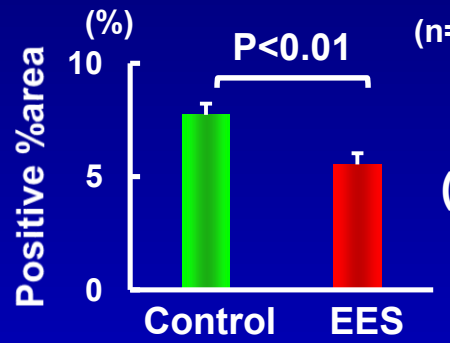
(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

Results (3) Enhanced inflammatory changes in the PVAT at EES edges compared with control sites



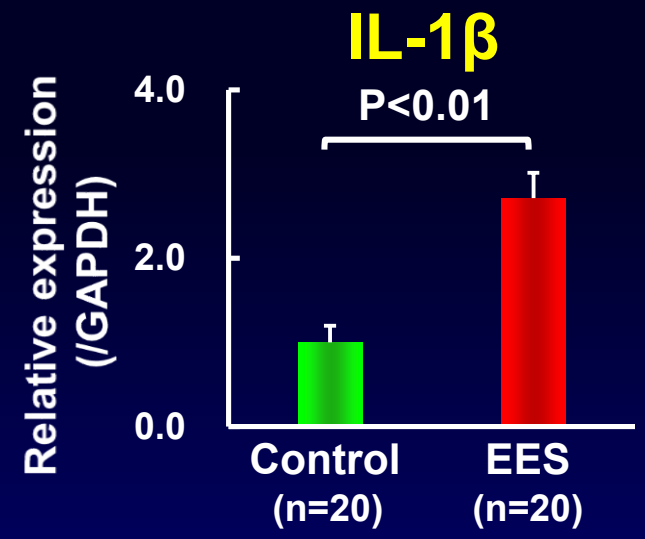


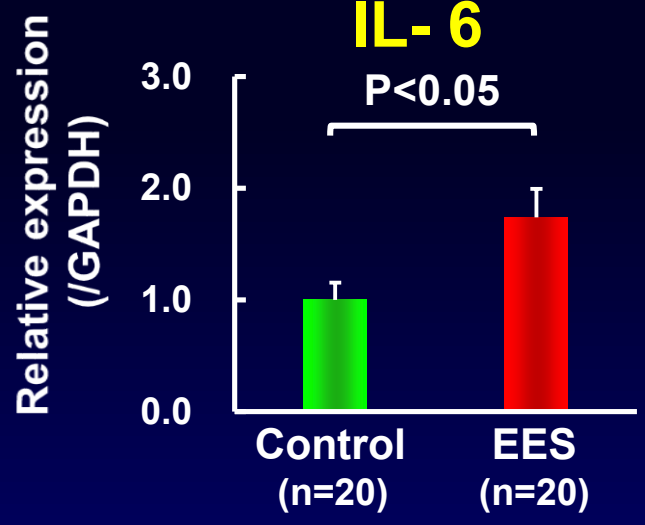


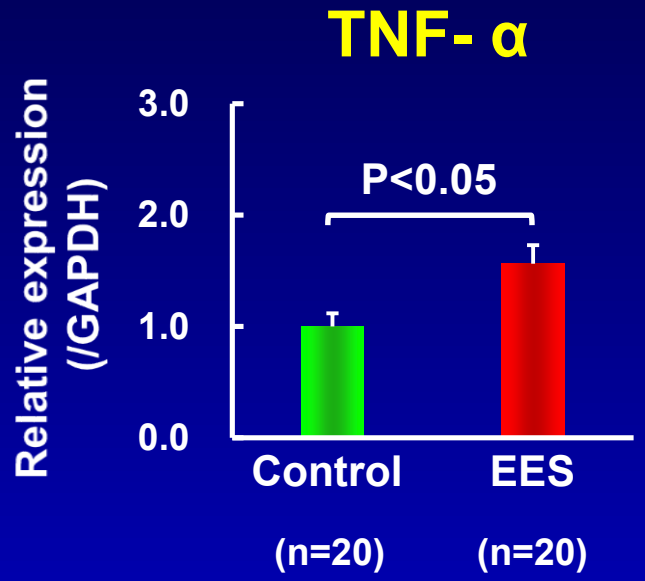


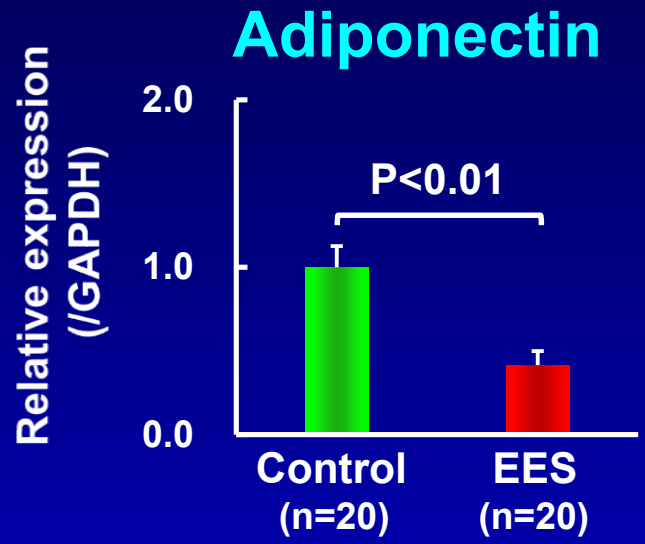
(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

Results (4) Enhanced mRNA expressions of inflammatory cytokines in the PVAT at EES edges compared with control sites



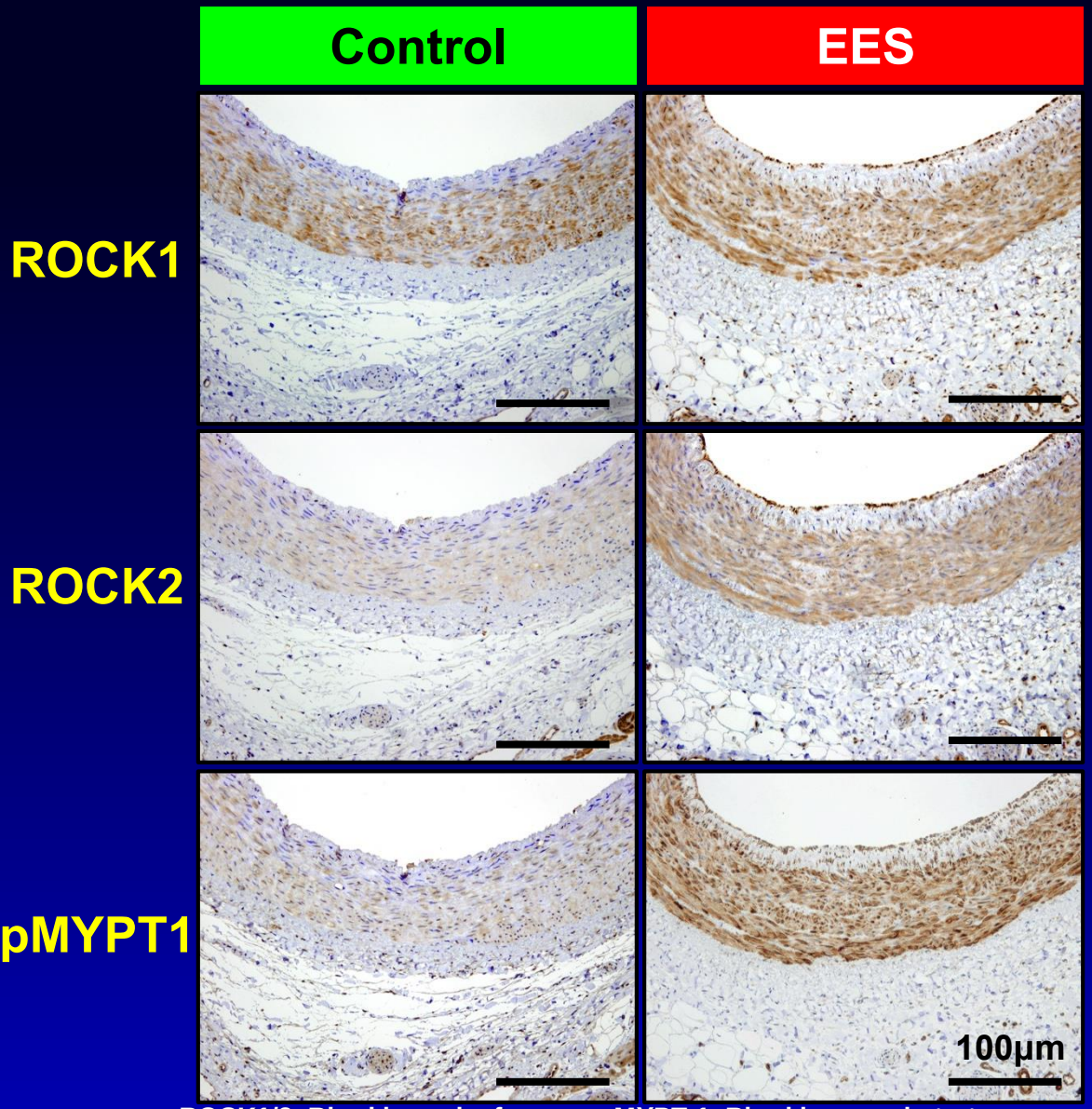




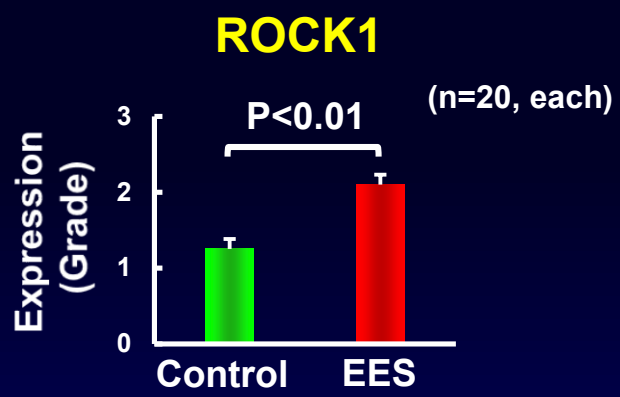


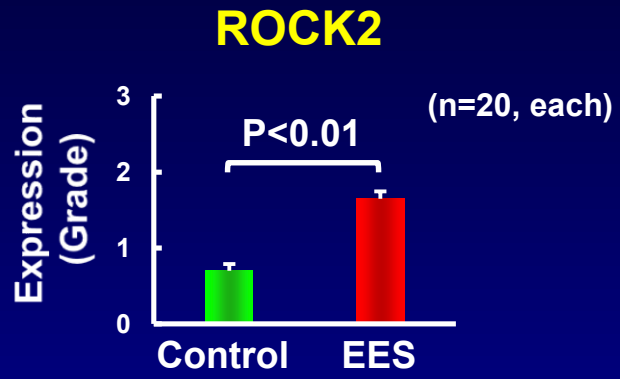
(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

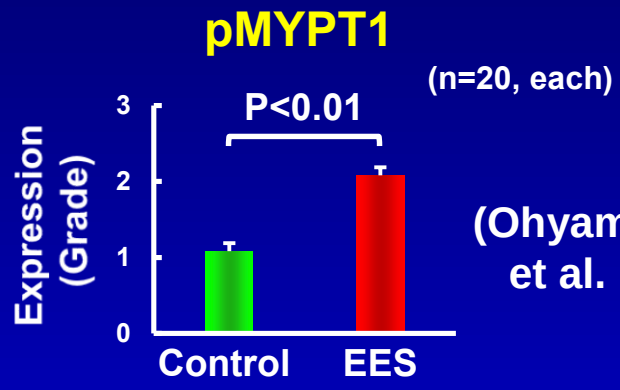
Results (5) Enhanced expression and activity of Rho-kinase at EES edges compared with control sites



ROCK1/2: Rho-kinase isoforms pMYPT-1: Rho-kinase substrate

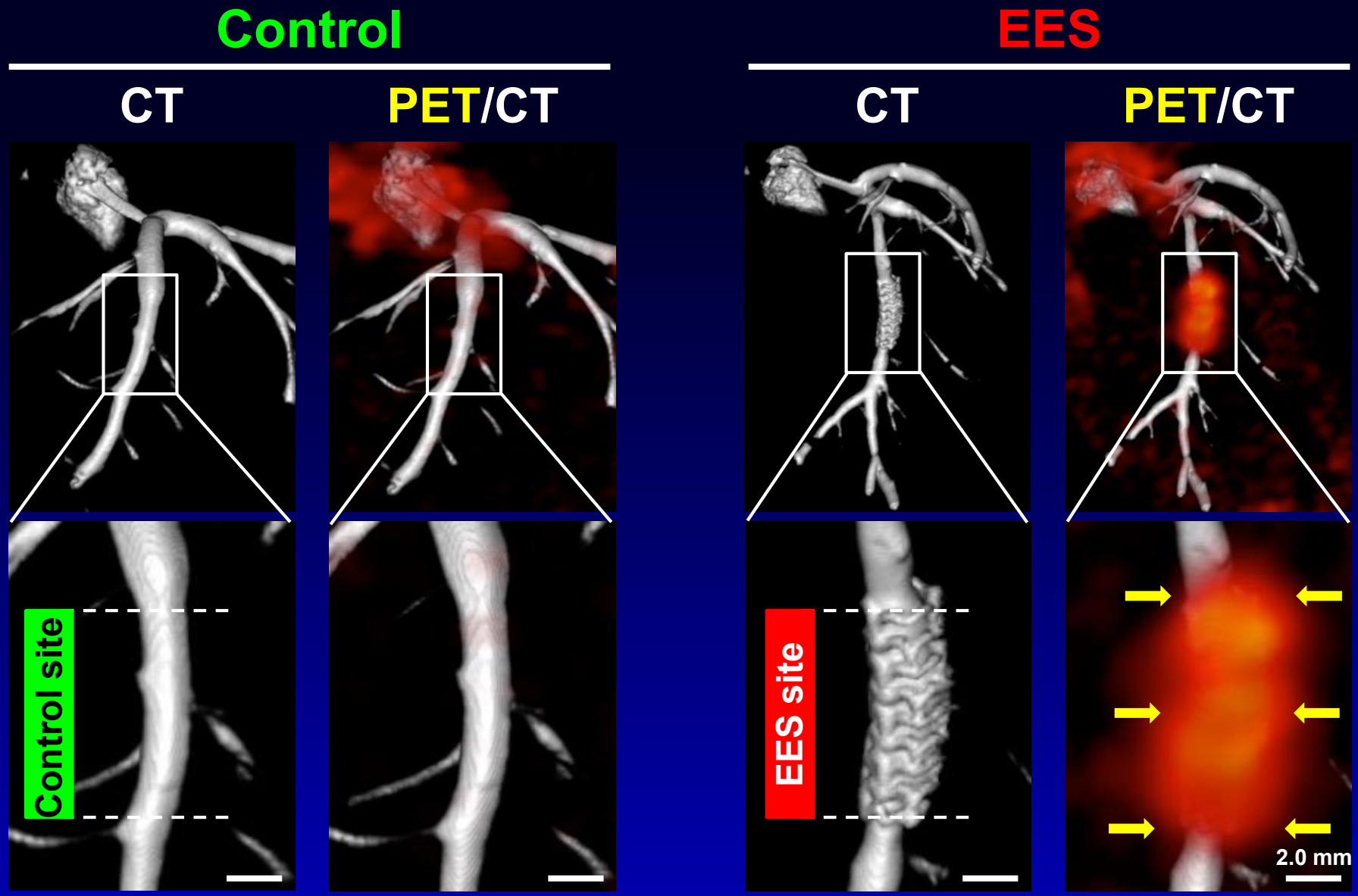






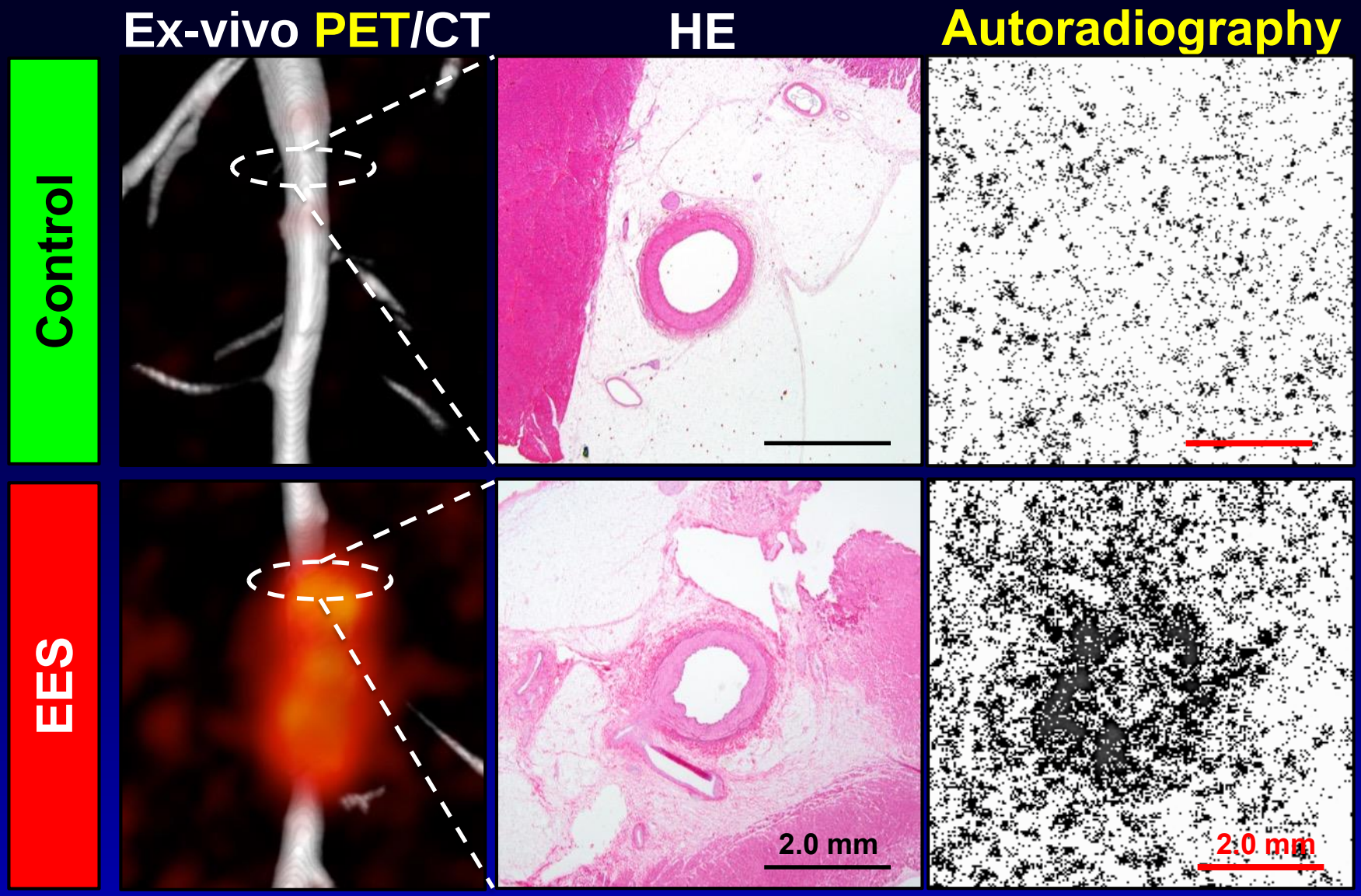
(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

Results (6) Enhanced ^{18}F-FDG uptake at EES sites compared with control sites in ex-vivo PET/CT



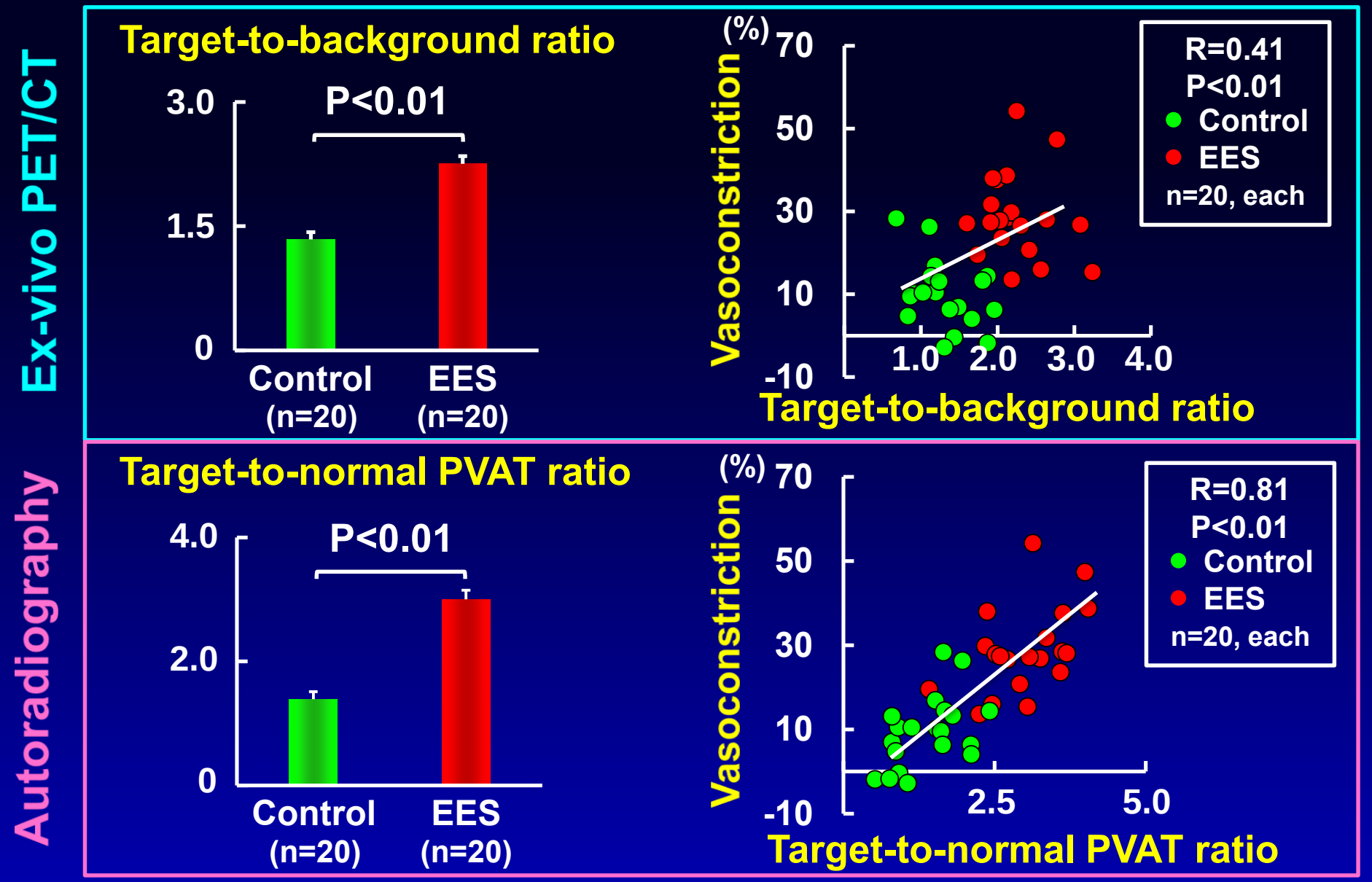
(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

Results (7) Enhanced ^{18}F-FDG accumulation at EES edges compared with control sites in autoradiography



(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

Results (8) Enhanced ^{18}F-FDG uptake in the PVAT at EES Edges compared with control sites in ex-vivo PET/CT, autoradiography



(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

Summary of the experimental study

1. **Inflammatory changes in the PVAT** and **Rho-kinase activity** were significantly enhanced at EES edges compared with control sites.

2. **^{18}F-FDG uptake in the PVAT** evaluated by ex-vivo PET/CT and autoradiography were significantly enhanced at EES edges compared with control sites.

3. There were significant **positive correlations** between **^{18}F-FDG uptake in the PVAT** and the extent of **coronary vasoconstriction**.

(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)

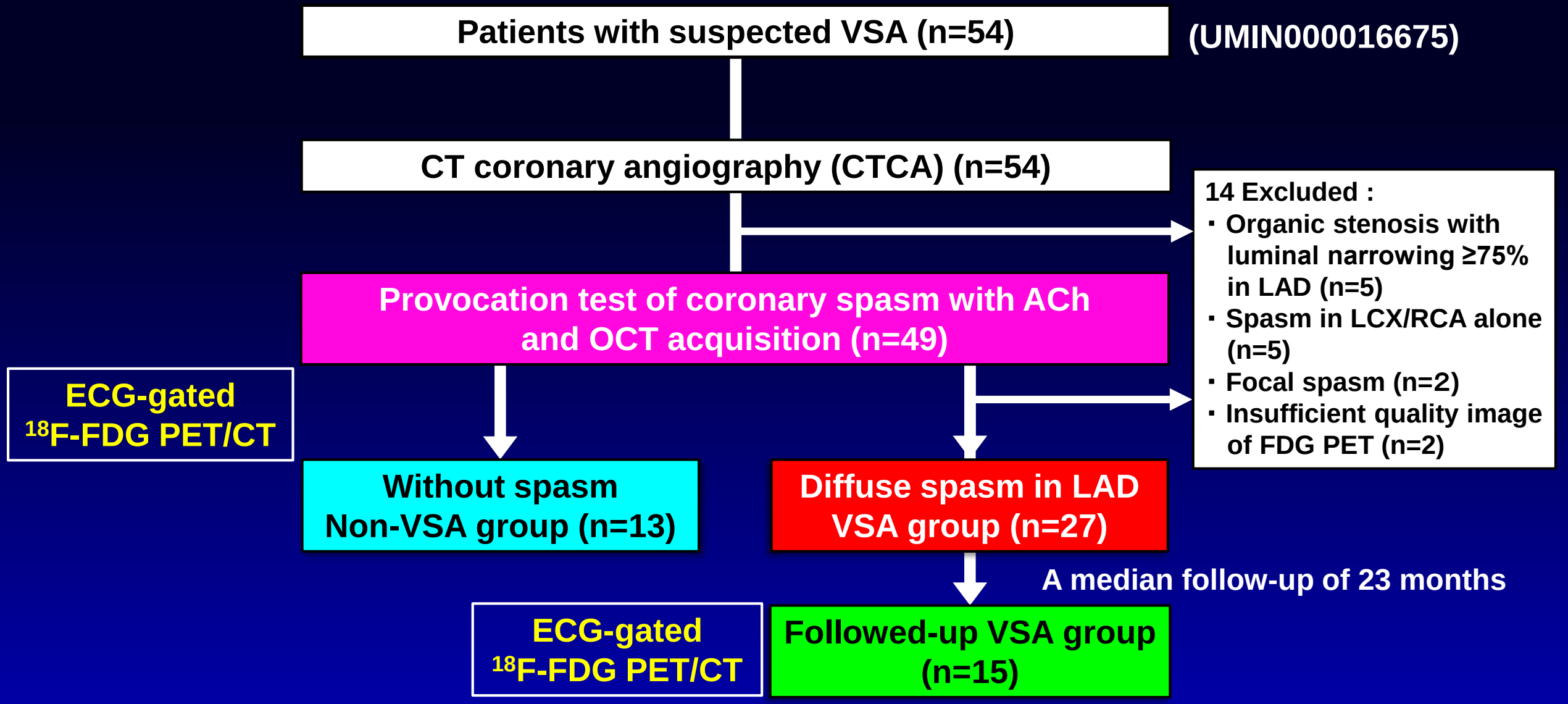
Clinical study

Coronary adventitial and PVAT inflammation in patients with vasospastic angina

-A multi-modality imaging study-

(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol.* 2018.)

Methods: Study flow



(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

Results (1) Baseline patient characteristics ①

	Non-VSA (n=13)	VSA (n=27)	P value
Age, years	65.4±3.3	62.1±2.1	0.40
Male, n (%)	8 (61)	16 (59)	0.89
Body weight, kg	59.1±2.4	59.5±3.5	0.93
Body mass index, kg/m^2	22.1±0.7	22.7±1.0	0.55
Percent body fat, %	24.4±2.0	26.1±1.4	0.49
Hypertension, n (%)	5 (38)	11 (41)	0.89
Diabetes mellitus, n (%)	1 (8)	2 (7)	0.97
LDL cholesterol, mg/dL	109.2±8.8	106.9±4.9	0.81
Current smoker, n (%)	5 (38)	11 (41)	0.88
Positive family history of CVD, n (%)	3 (23)	2 (8)	0.18
LVEF, %	68.6±1.8	66.9±1.1	0.44

(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

Results (2) Baseline patient characteristics ②

	Non-VSA (n=13)	VSA (n=27)	P value
Cardiac markers			
hs-CRP, mg/dl	0.06±0.31	0.05±0.01	0.55
BNP, pg/ml	20.4±4.1	21.2±3.8	0.89
Troponin I, μg/l	0.01±0.001	0.01±0.002	0.72
Medical treatments, n (%)			
CCB	8 (62)	17 (63)	0.93
Long-acting nitrate	2 (15)	6 (22)	0.61
K channel opener	2 (8)	9 (14)	0.39
ACE-I or ARB	5 (38)	6 (22)	0.41
Beta-blocker	0 (0)	6 (22)	0.07
Statin	4 (31)	9 (33)	0.87
Anti-platelet	3 (23)	11 (41)	0.27

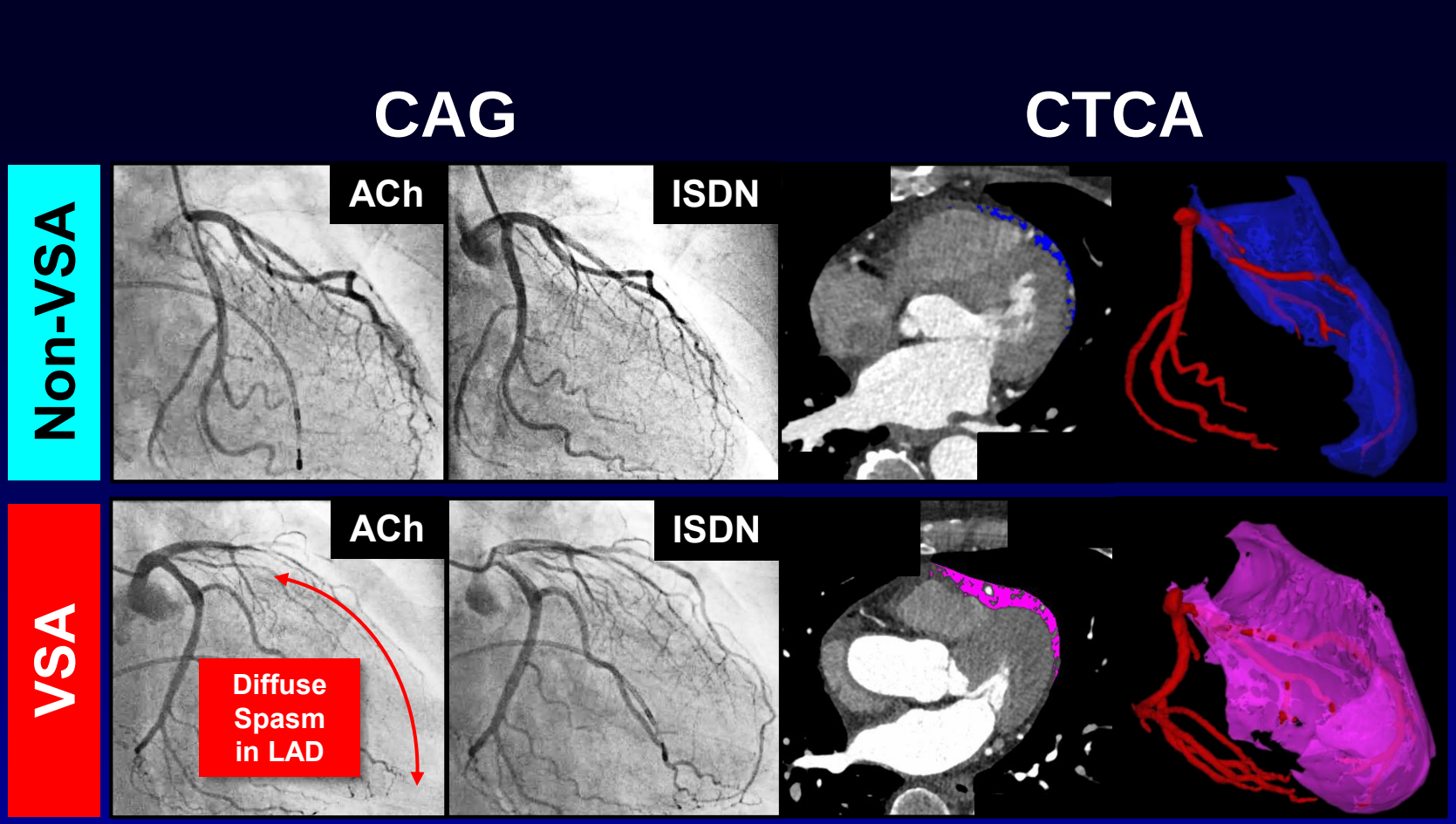
(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

Results (3) Angiographic assessment

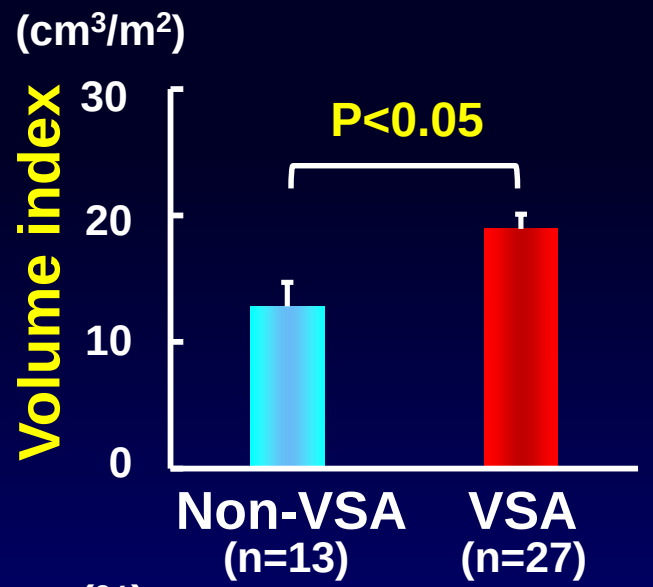
		Non-VSA (n=13)	VSA (n=27)	P value
Organic stenosis, n (%)				
LAD	25%	5 (38)	8 (30)	0.58
	50%	3 (23)	5 (19)	0.74
LCX	25%	1 (8)	2 (7)	0.97
	50%	0 (0)	1 (4)	0.48
	75%	1 (8)	1 (4)	0.59
RCA	25%	3 (23)	5 (19)	0.74
	50%	0 (0)	1 (4)	0.48
	75%	0 (0)	1 (4)	0.48
Coronary spasm provocation test				
Maximum dose of acetylcholine, μg/kg		100.0±0.0	73.0±8.1	N/A
Multi-vessel spasm		-	6 (22)	N/A

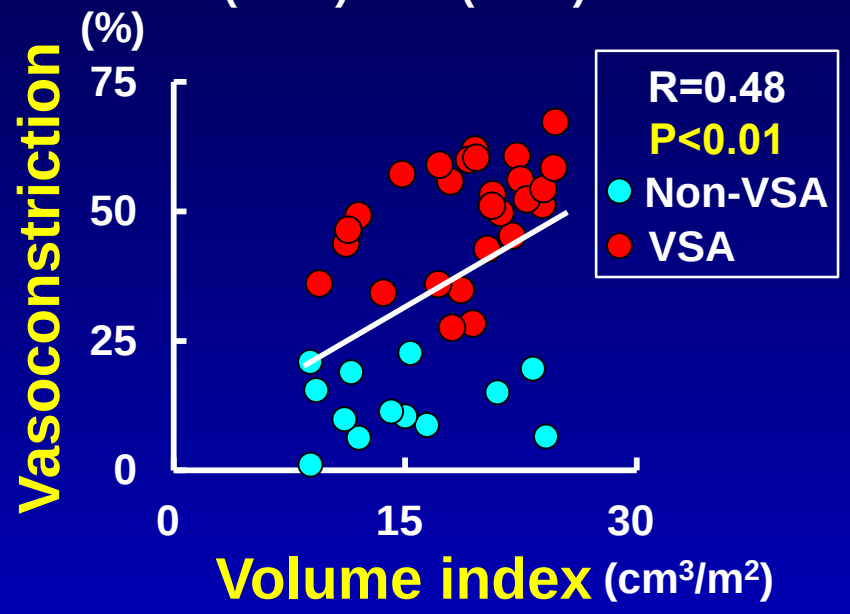
(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

Results (4) Increased PVAT volume at the spastic coronary segment



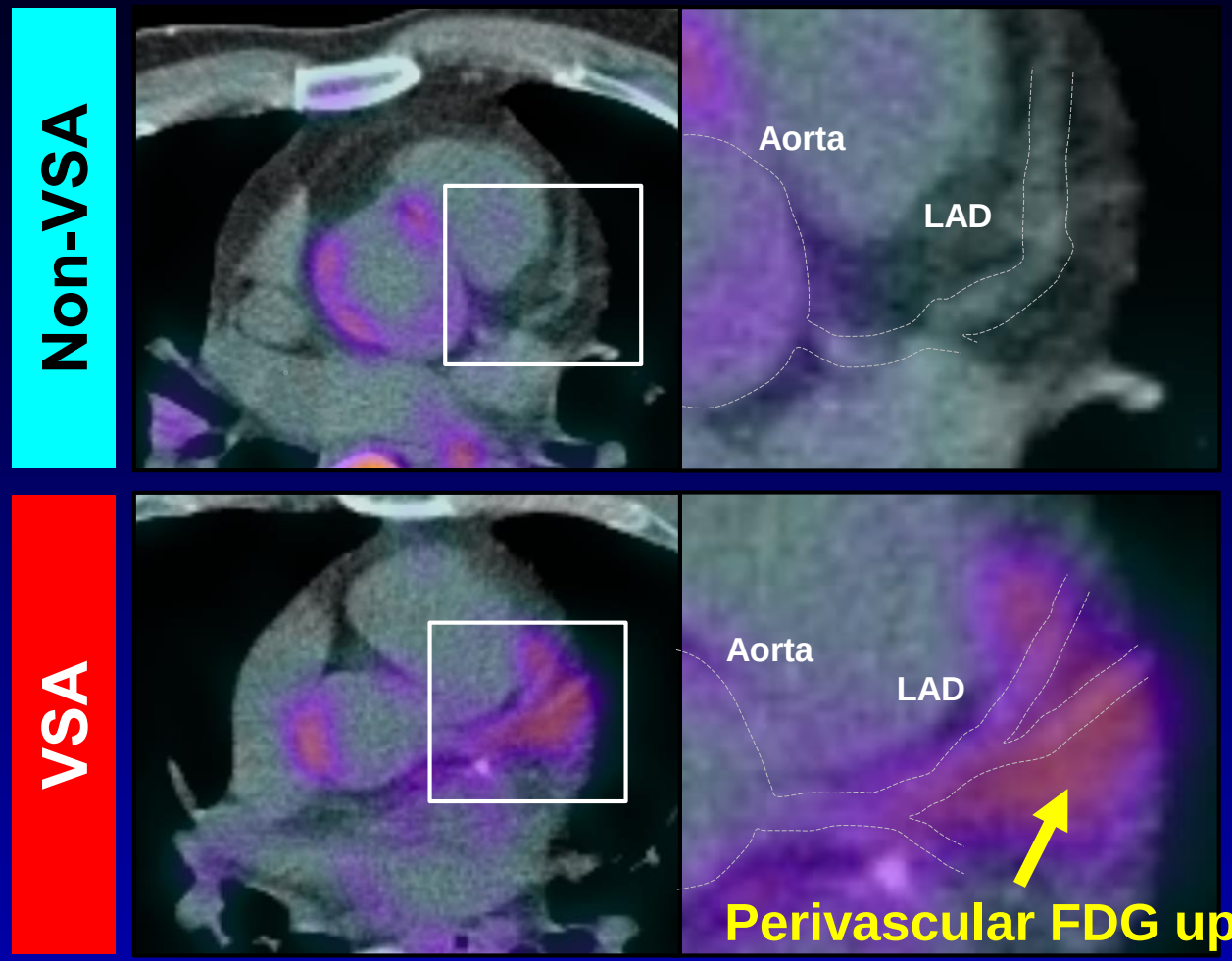
(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

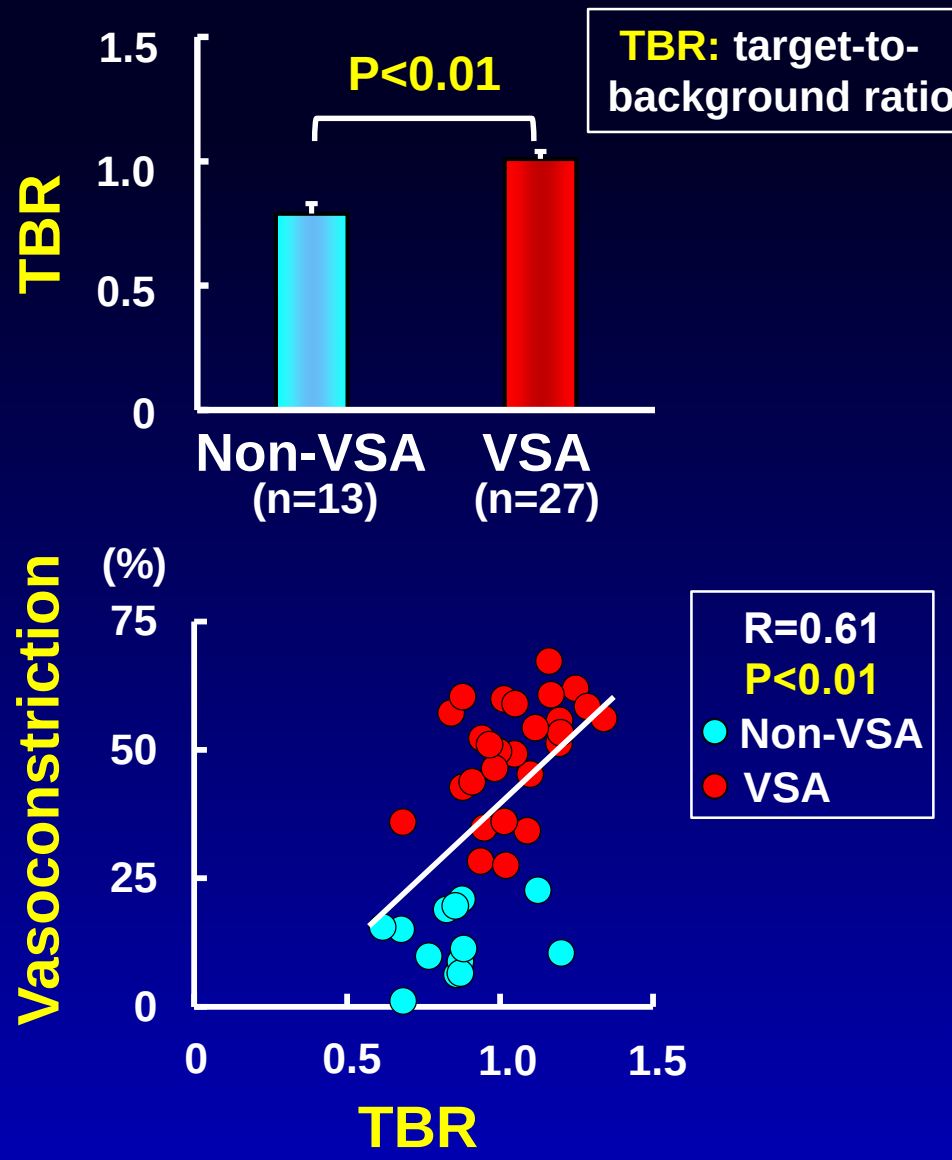




Results (5) Enhanced perivascular FDG uptake in VSA patients

ECG-gated ^{18}F-FDG PET/CT





(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

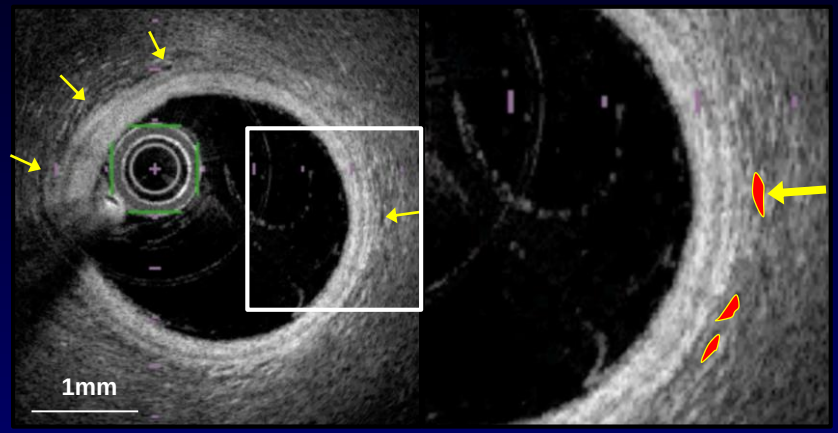
Results (7) Enhanced adventitial VV formation associated with PVAT volume and perivascular FDG uptake in VSA patients

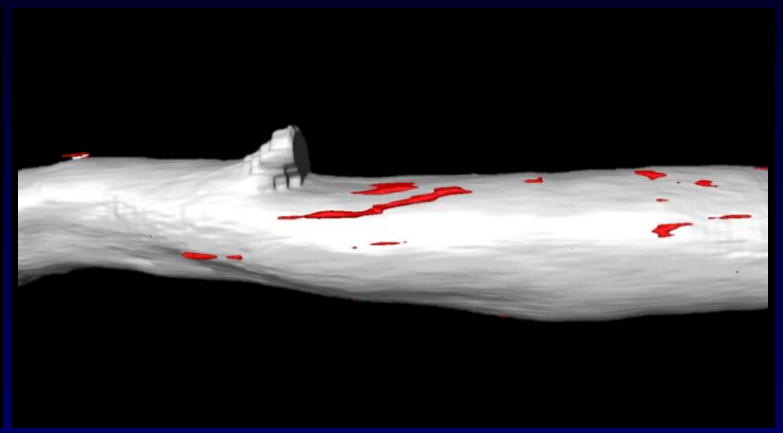
Cross-sectional OCT

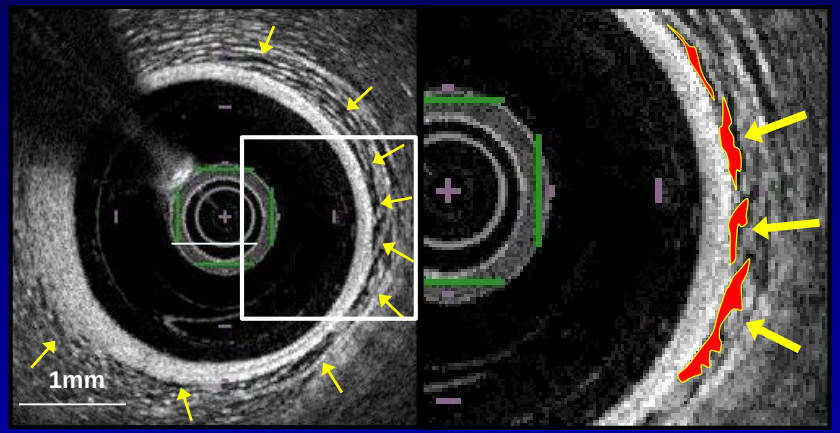
3D-OCT

Non-VSA

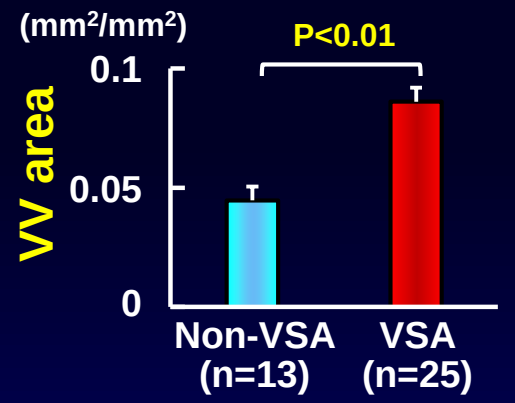
VSA

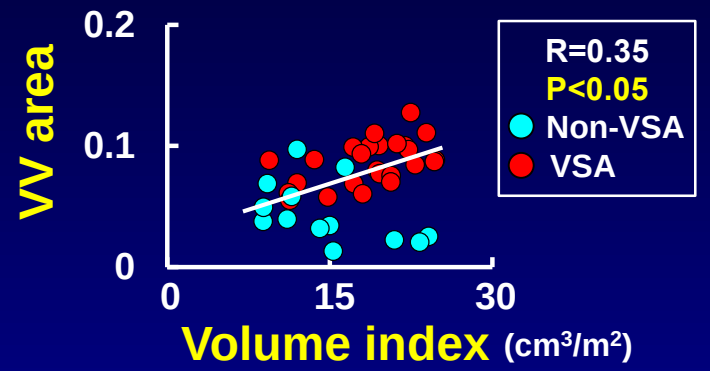


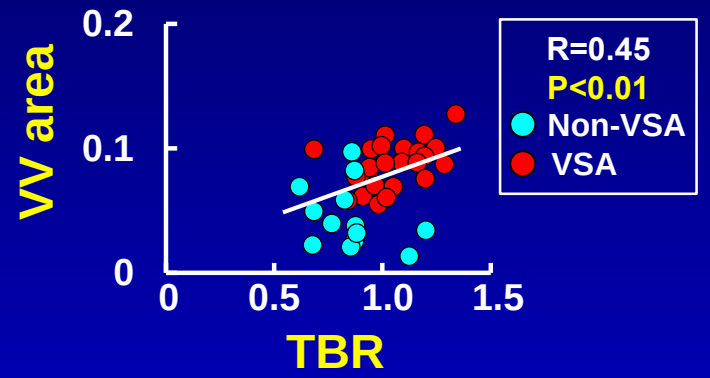




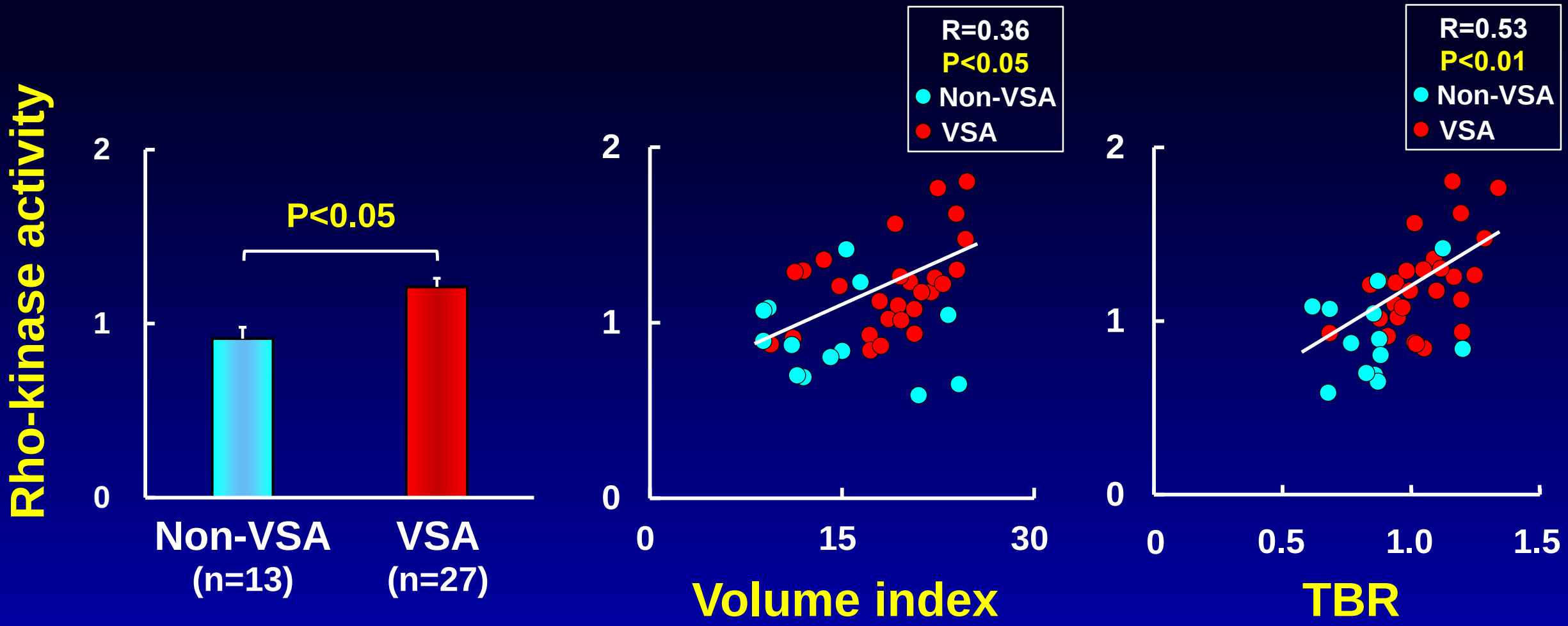
(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)







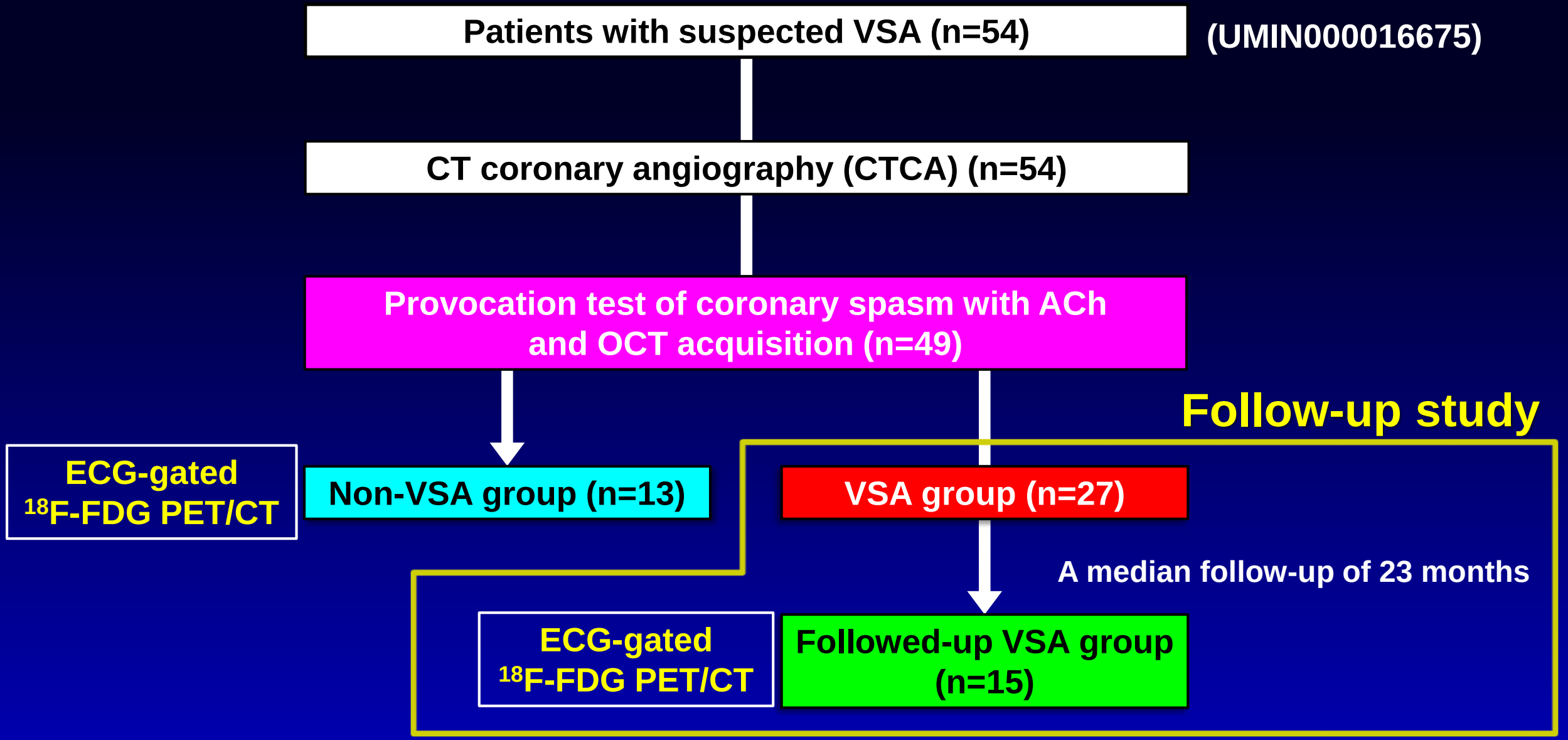
Results (8) Enhanced Rho-kinase activity associated with PVAT volume and perivascular FDG uptake in VSA patients



(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

Follow-up study

Study flow


Patients with suspected VSA (n=54)
(UMIN000016675)
CT coronary angiography (CTCA) (n=54)
Provocation test of coronary spasm with ACh and OCT acquisition (n=49)
Follow-up study
ECG-gated ^{18}F-FDG PET/CT
Non-VSA group (n=13)
VSA group (n=27)
A median follow-up of 23 months
ECG-gated ^{18}F-FDG PET/CT
Followed-up VSA group (n=15)

Results (9) Baseline patient characteristics in the follow-up study

	Followed-up VSA (n=15)	Non-Followed-up VSA (n=12)	P value
Age, years	64.1±2.6	59.6±3.3	0.32
Male, n (%)	8 (53.3)	8 (66.7)	0.48
Body weight, kg	57.7±2.8	61.6±3.3	0.40
Body mass index, kg/m^2	22.5±0.8	23.0±0.97	0.72
Percent body fat, %	24.7±1.4	28.0±2.6	0.29
Hypertension, n (%)	6 (40)	5 (42)	0.93
Diabetes mellitus, n (%)	0 (0)	2 (17)	0.10
LDL cholesterol, mg/dL	104.7±5.9	109.6±8.1	0.64
Current smoker, n (%)	3 (20)	3 (25)	0.76
Positive family history of CVD, n (%)	1 (7)	1 (8)	0.91
LVEF, %	67.1±1.3	66.7±1.8	0.88

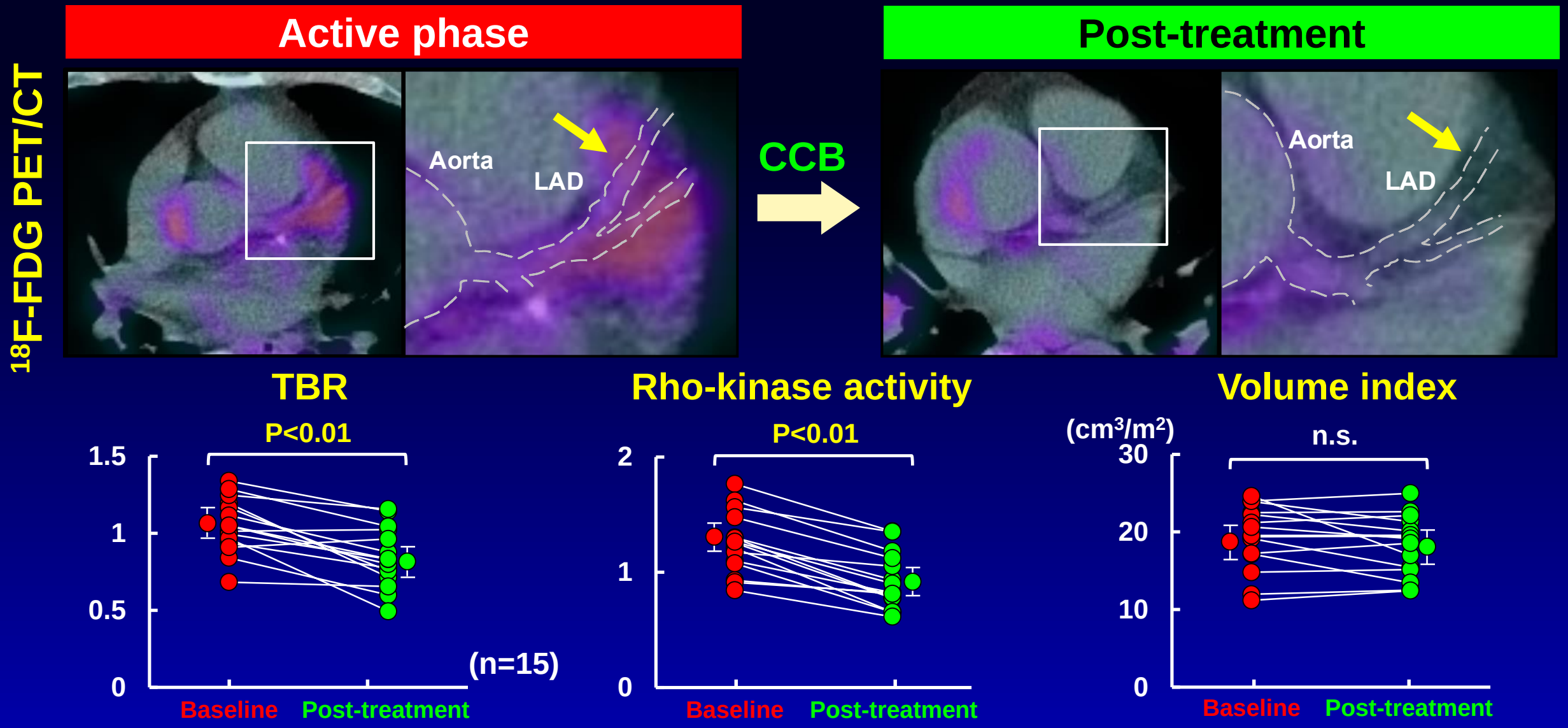
(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

Results (10) Medical treatment during follow up

	Baseline	Post-treatment	P value
CCB	11 (73)	15 (100)	0.03
Long-acting nitrate	5 (33)	5 (33)	1.00
Potassium channel opener	2 (13)	4 (27)	0.39
ACE-I or ARB	2 (13)	3 (20)	0.62
Beta-blocker	4 (27)	4 (27)	1.00
Statins	4 (27)	7 (47)	0.26
Anti-platelet	7 (47)	6 (40)	0.71

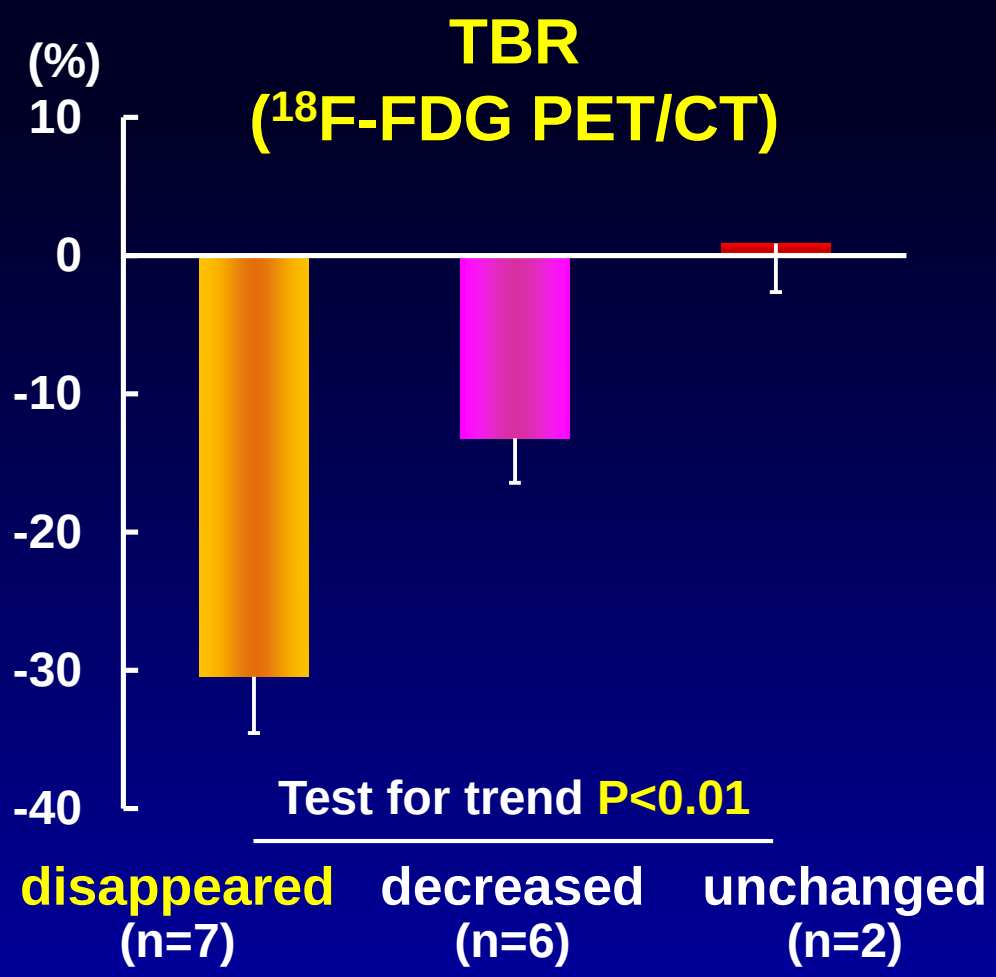
(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

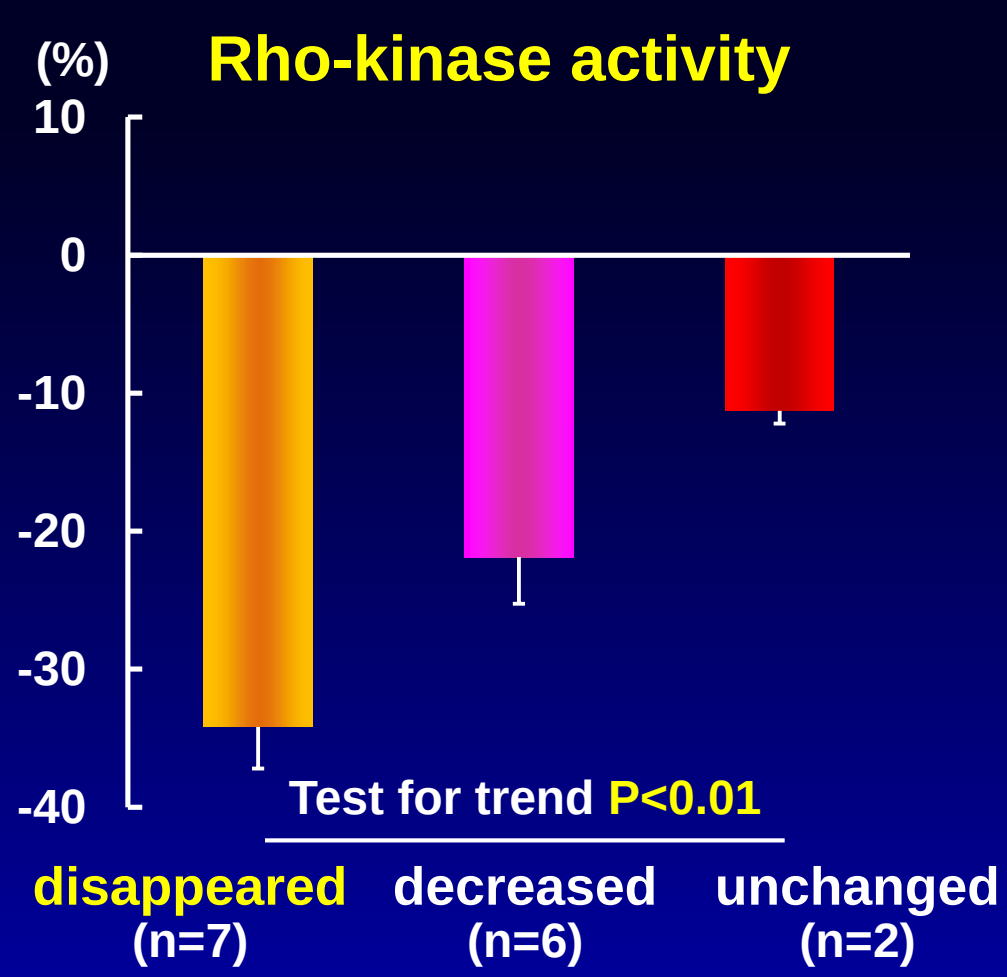
Results (11) Reduced perivascular FDG uptake and Rho-kinase activity after treatment with CCB in VSA patients



(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

Results (12) Improvement of angina symptoms associated with reduced perivascular FDG uptake and Rho-kinase activity after treatment with CCB





(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

Summary of the clinical study

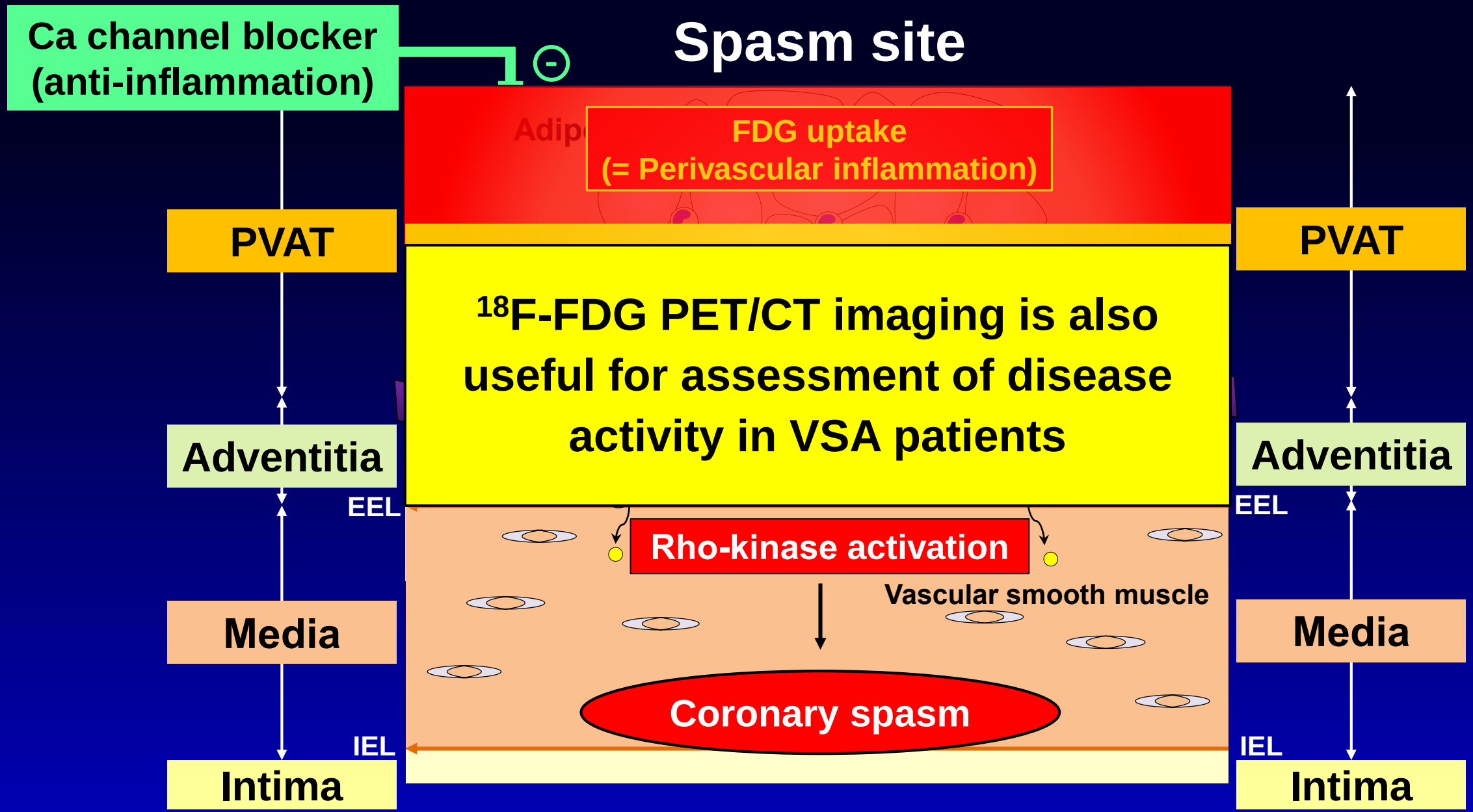
1. **PVAT volume** with CTCA and **perivascular FDG uptake** with ^{18}F-FDG PET/CT were significantly increased in the **VSA group** compared with the non-VSA group.

2. The extents of **PVAT volume** and **perivascular FDG uptake** were positively correlated with those of **adventitial VV formation** with OCT and **Rho-kinase activity** in all patients.

3. The levels of **perivascular FDG uptake** and **Rho-kinase activity** were significantly reduced after **long-term treatment with CCB** in the VSA group.

(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

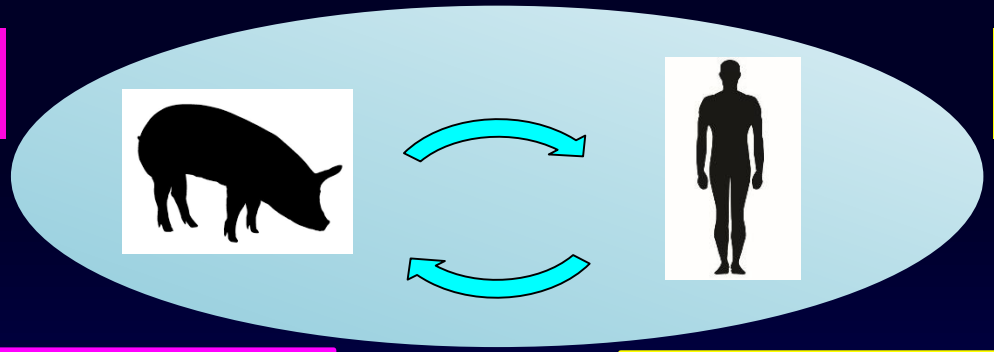
Discussion (1) Working model of the present study



Discussion (2) Translational research on the pathogenesis of coronary spasm

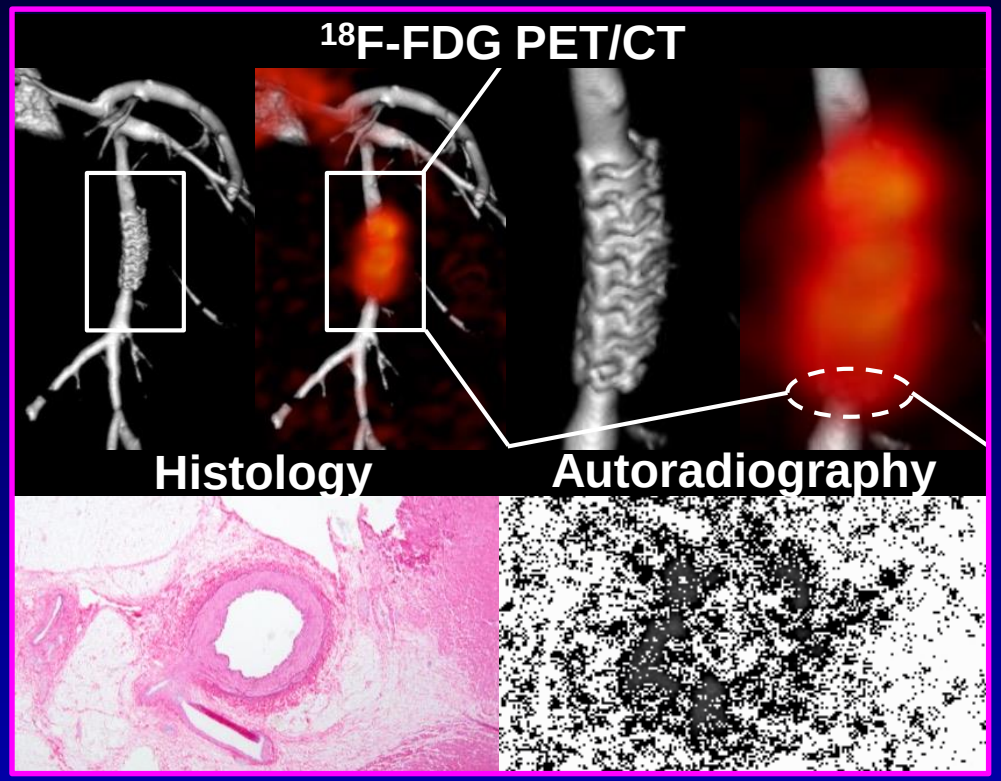
Basic research

Pig

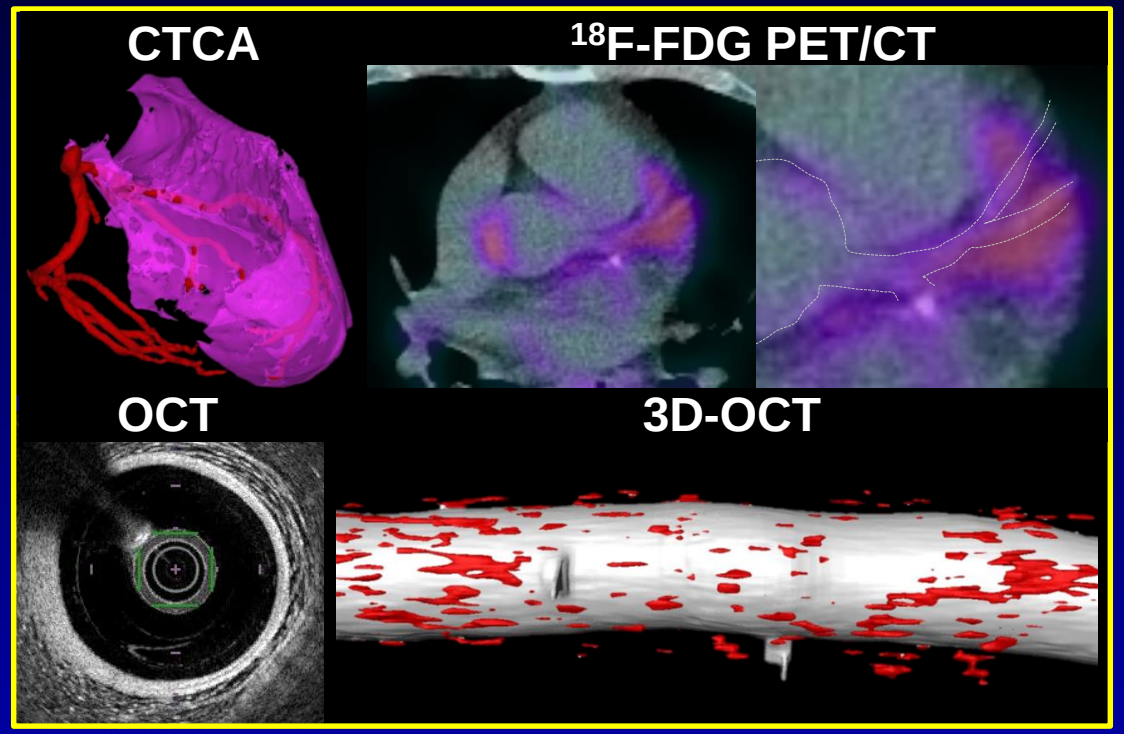


Clinical research

Human



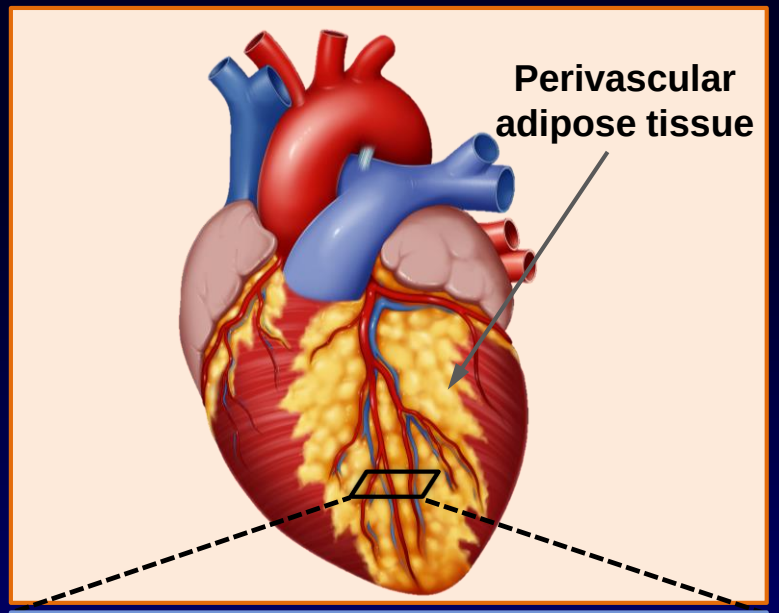
(Ohyama K, Shimokawa H, et al. *ATVB* 2017.)



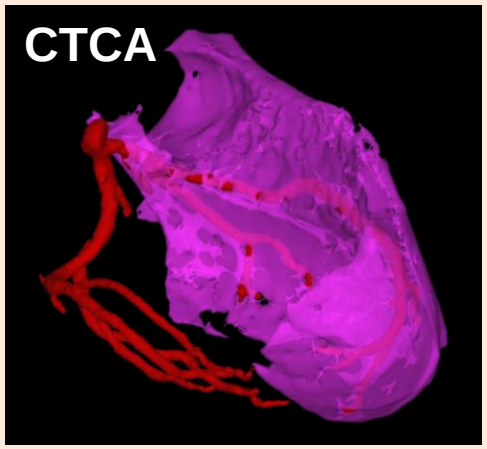
(Ohyama K, Shimokawa H, et al. *Circ J* 2016.)

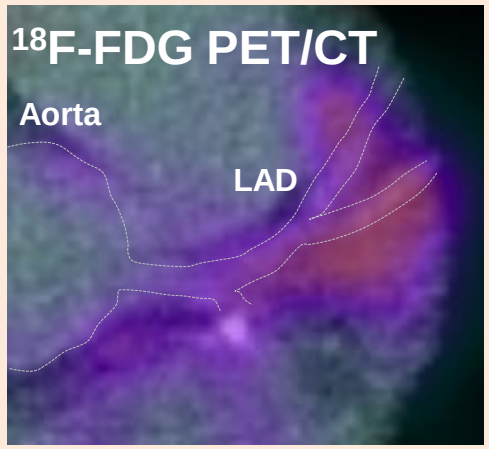
(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

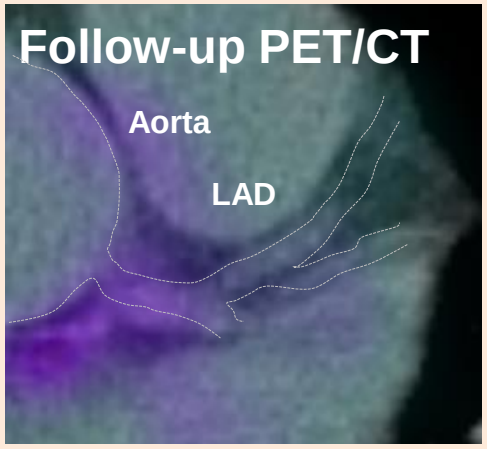
Discussion (3) Important role of perivascular inflammation as a potent substrate for coronary spasm with multi-modality imagings



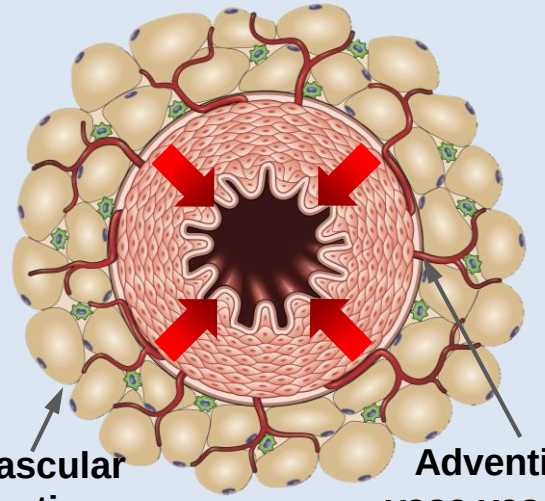
Cardiac imaging from outside



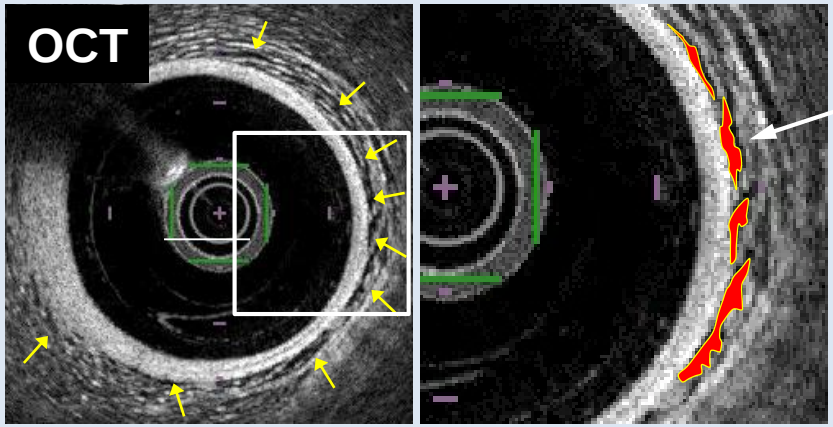


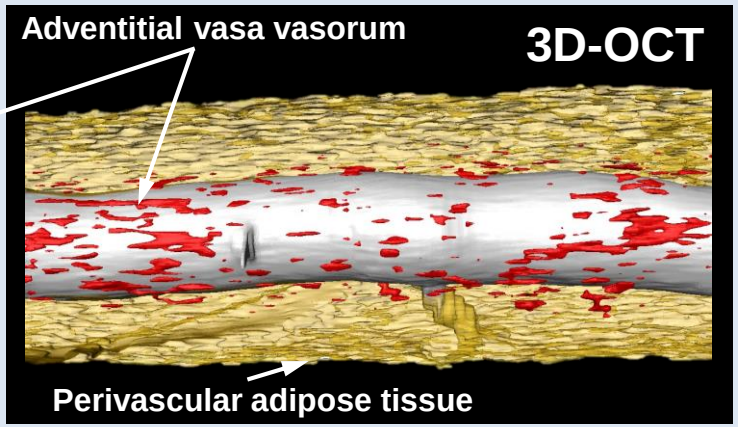


Coronary spasm



Intravascular imaging from inside





(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

Conclusions

These findings provide the first direct evidence that perivascular inflammation could be the substrate for coronary spasm, which can be improved after long-term treatment with CCB and that ^{18}F-FDG PET/CT is useful for assessment of disease activity in VSA patients.

(Ohyama K, Shimokawa H, et al. *J Am Coll Cardiol* 2018.)

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Thank you
for
your kind attention