

Studies of non-clinical pathophysiological models and pathological evaluation techniques to reduce the toxicity of anti-cancer drugs

- Cardiotoxicity of microtubule polymerization inhibitors -

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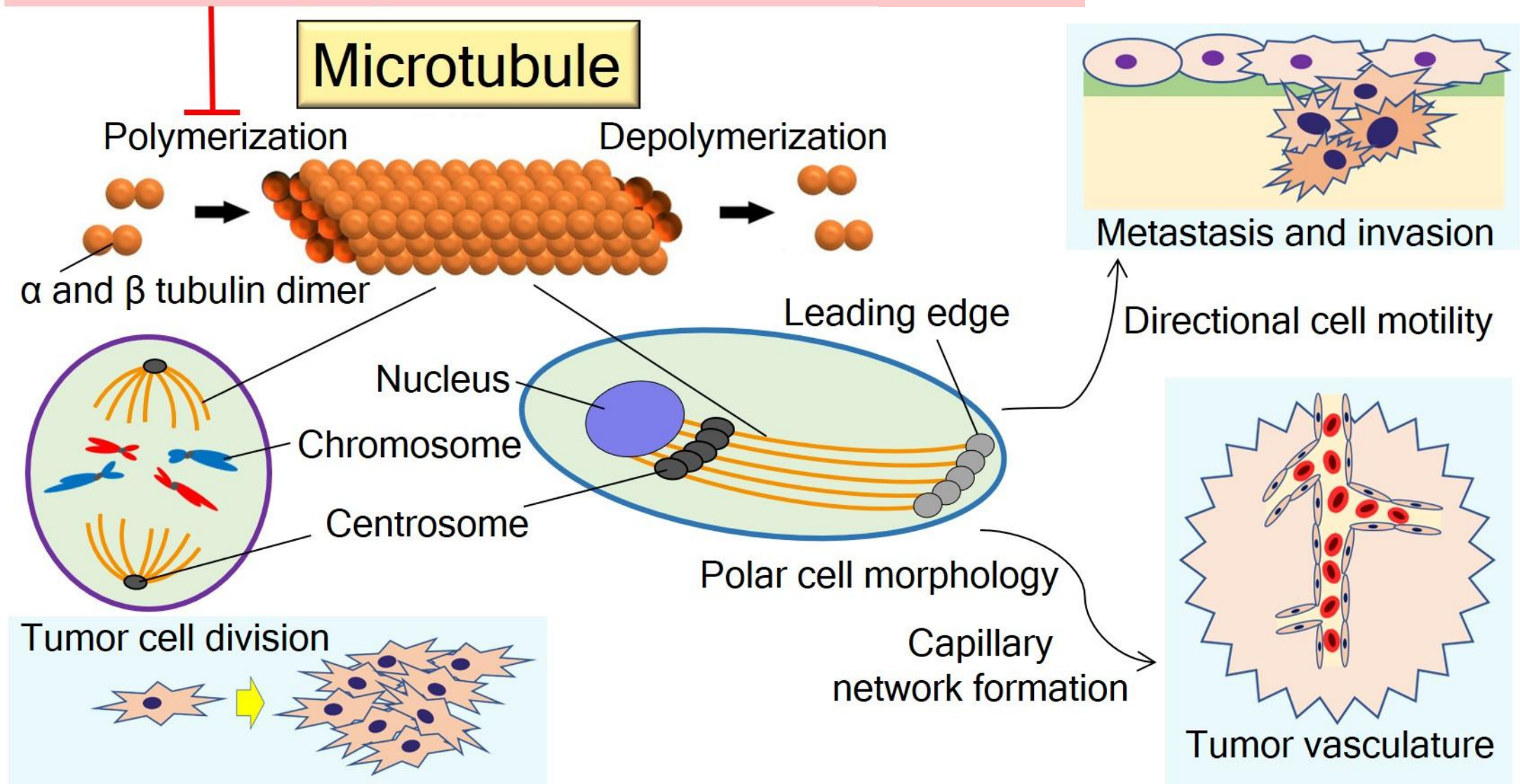
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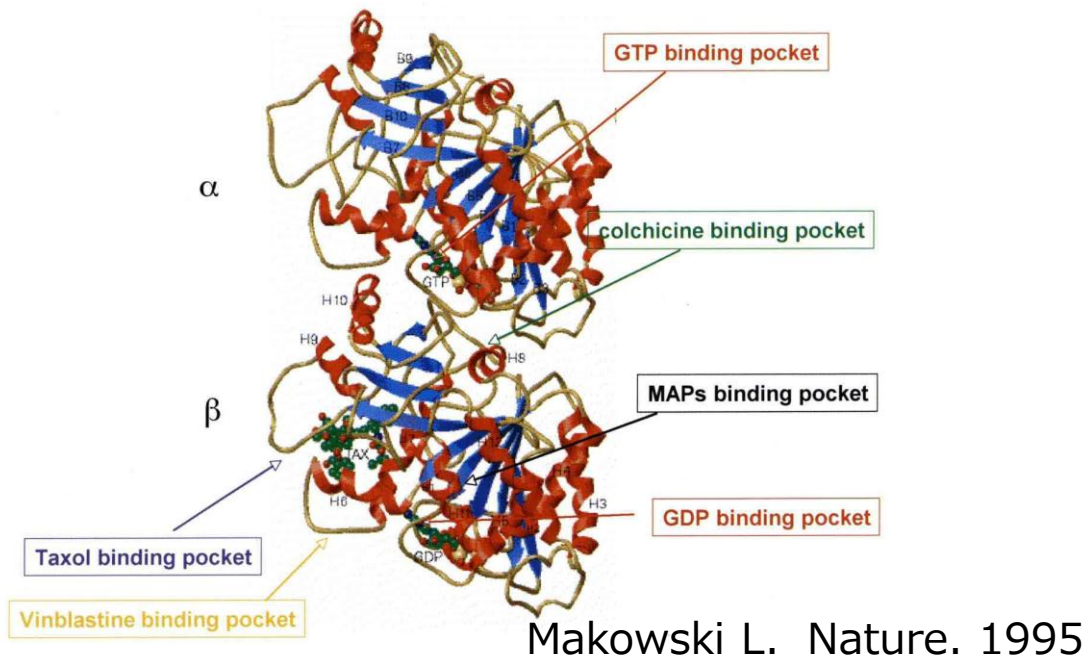
8 November 2025

the 23rd Annual Meeting of the Asian Association of Veterinary Schools (AAVS)

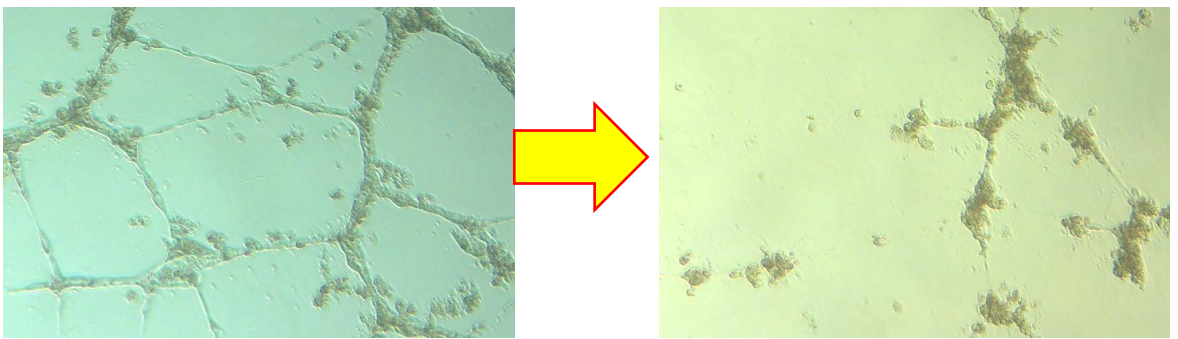
Microtubule polymerization inhibitors (MPIs)



MPIs as anti-cancer drugs



Destruction of vascular endothelial cells by Combretastatin A4 (CA4DP, a colchicine analogue)



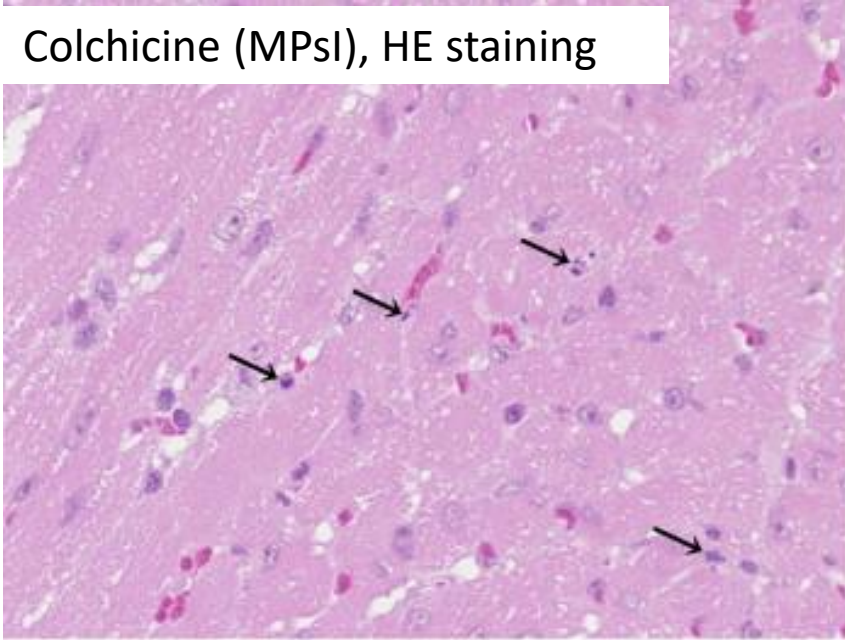
Nagashima Y, Tochinal R*, et al. J Toxicol Pathol. 2023.

Drug	Status	Cancer type	Reference
Vinblastine	Approved by FDA in 1961	Generalized Hodgkin's disease, lymphocytic lymphoma, histiocytic lymphoma, mycosis fungoides, advanced carcinoma of the testis, Kaposi's sarcoma, Letterer-Siwe disease, choriocarcinoma, carcinoma of the breast	United States National Library of Medicine, 2023b-e
Vincristine	Approved by FDA in 1963	Acute leukemia, Hodgkin's disease, non-Hodgkin's malignant lymphomas, rhabdomyosarcoma, neuroblastoma, Wilms' tumor	
Vinorelbine	Approved by FDA in 1994	Locally advanced or metastatic non-small cell lung cancer	
Eribulin	Approved by FDA in 2016	Metastatic breast cancer, liposarcoma	
Combretastatin A4 phosphate (Fosbretabulin) (CA4DP)	Clinical trials	Ovarian cancer, neuroendocrine tumors, thyroid cancer, head and neck cancer, fallopian tube carcinoma, primary peritoneal carcinoma, solid tumor, central nervous system tumor	United States National Library of Medicine, 2023a
AVE8062 (Ombrabulin)	Clinical trials	Malignant neoplasm, solid tumor, sarcoma, non-small cell lung cancer, ovarian cancer	
Combretastatin A1 phosphate (OXi4503)	Clinical trials	Acute myelogenous leukemia, neoplasm metastasis, solid tumor	
ZD6126	Clinical trials	Renal cell carcinoma, colorectal cancer	
MPC-6827	Clinical trials	Glioblastoma, melanoma, Brain neoplasm, Refractory solid tumor	Tochinal R*, et al. J. Appl. Toxicol. 2024
NPI-2358 (Plinabulin)	Clinical trials	Solid tumor, lymphoma, Non-small cell lung cancer, small cell lung cancer, multiple myeloma, bladder carcinoma	
2-methoxyestradiol (Panzem)	Clinical trials	Multiple myeloma, solid tumor, carcinoid tumor, glioblastoma, ovarian cancer, prostate cancer, renal cell carcinoma	

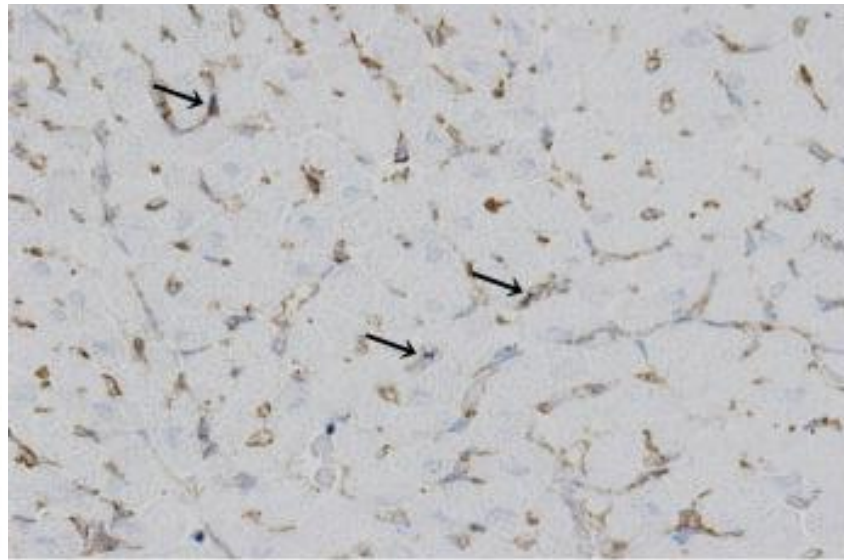
Strongly Cardiotoxic...

Microvascular endothelial cells in the heart exhibit high sensitivity to MPIs.

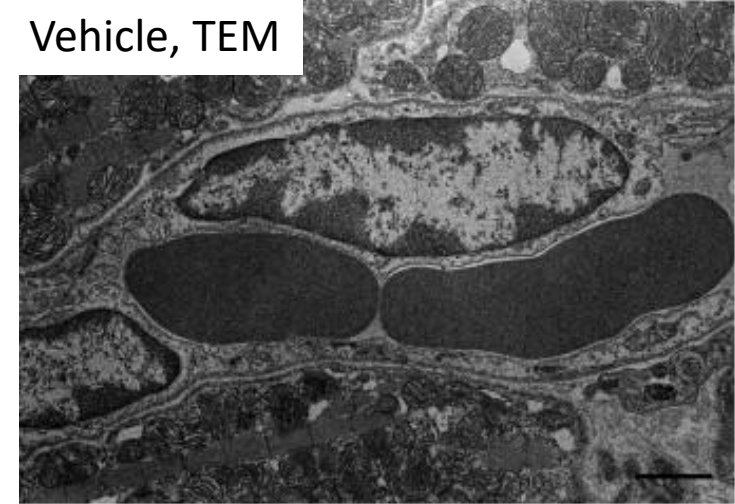
Colchicine (MPI), HE staining



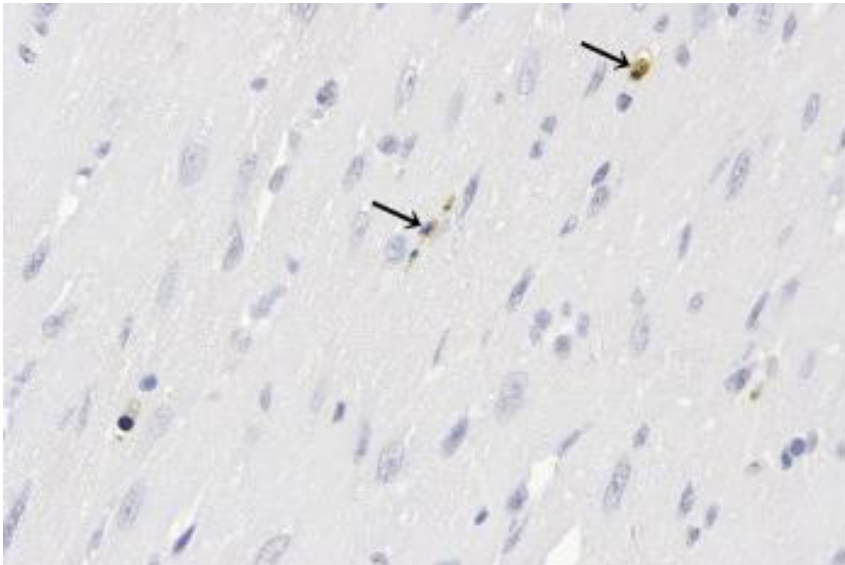
CD34, marker for vascular endothelial cells



Vehicle, TEM



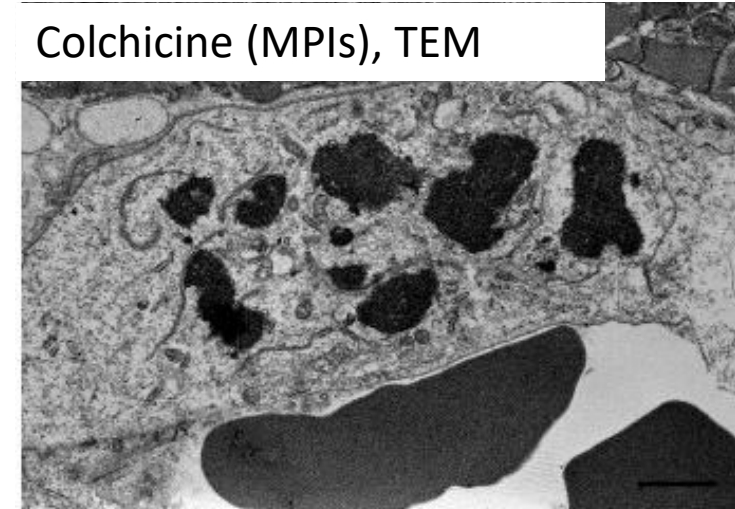
TUNEL, marker for apoptosis



pimonidazole, marker for hypoxia



Colchicine (MPIs), TEM

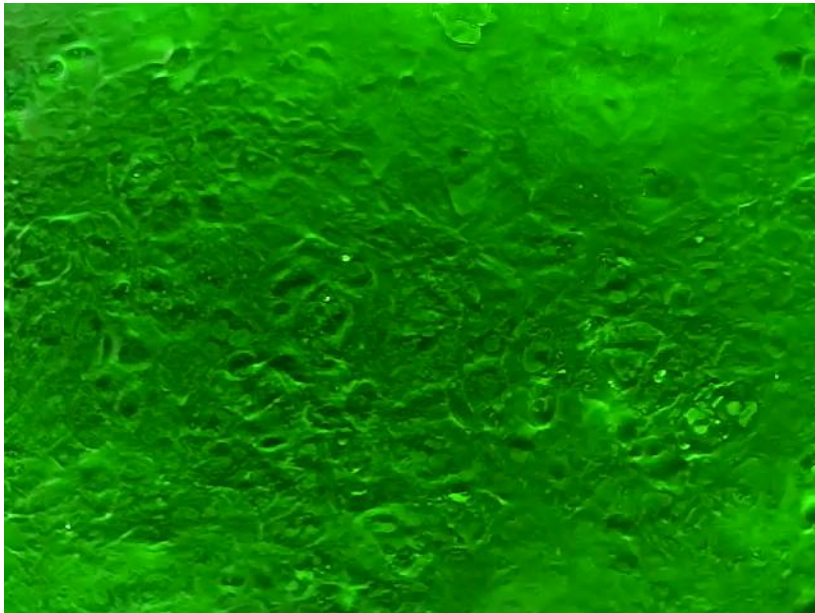


Tochinai R*, et al.
Exp Toxicol Pathol. 2013.

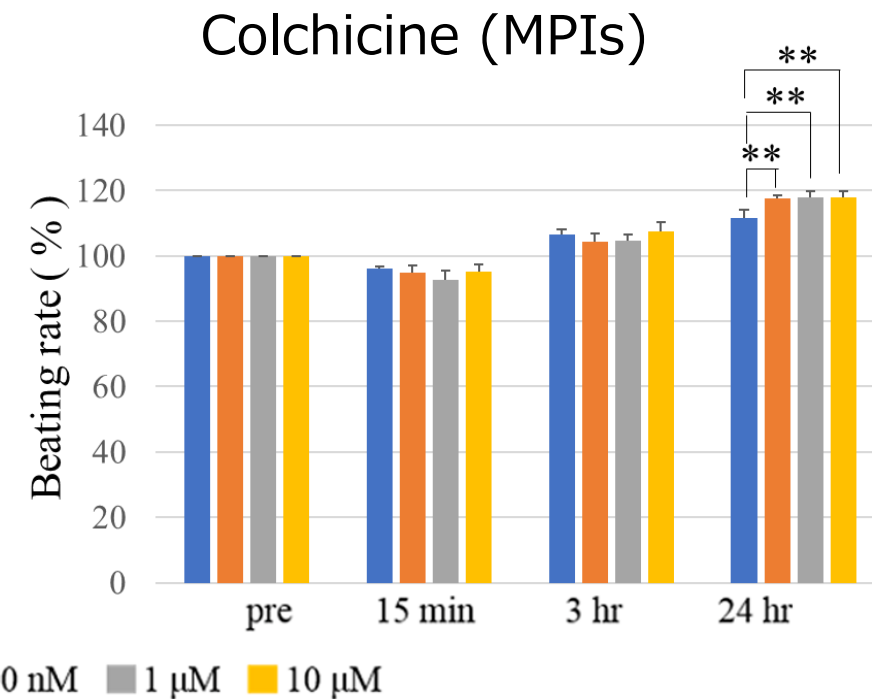
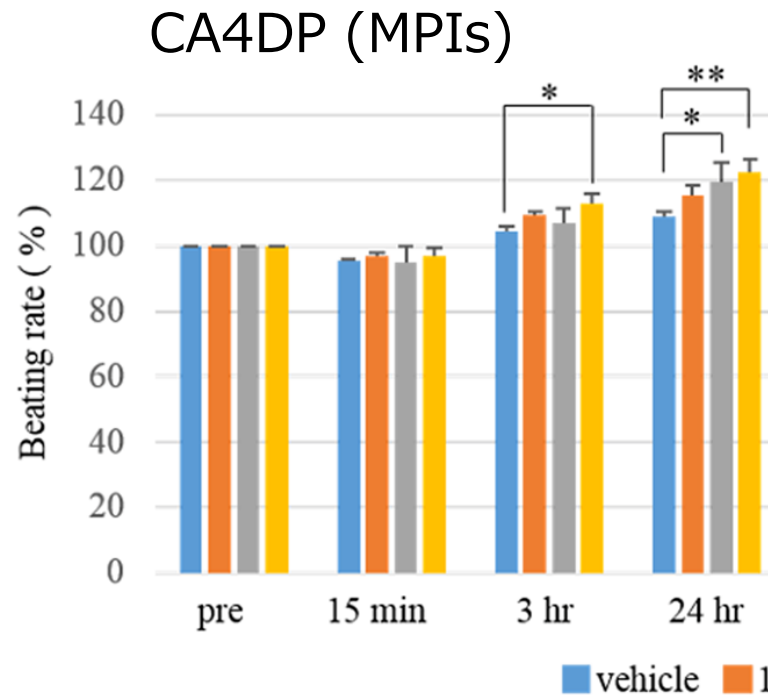
MPIs induce increase in heart cell beating

I used human induced pluripotent stem cell-derived cardiomyocytes (hiPS-CMs) to examine the possibility that CA4DP have direct toxicity in cardiomyocytes.

hiPS-CMs
(iCell[®] cardiomyocytes)



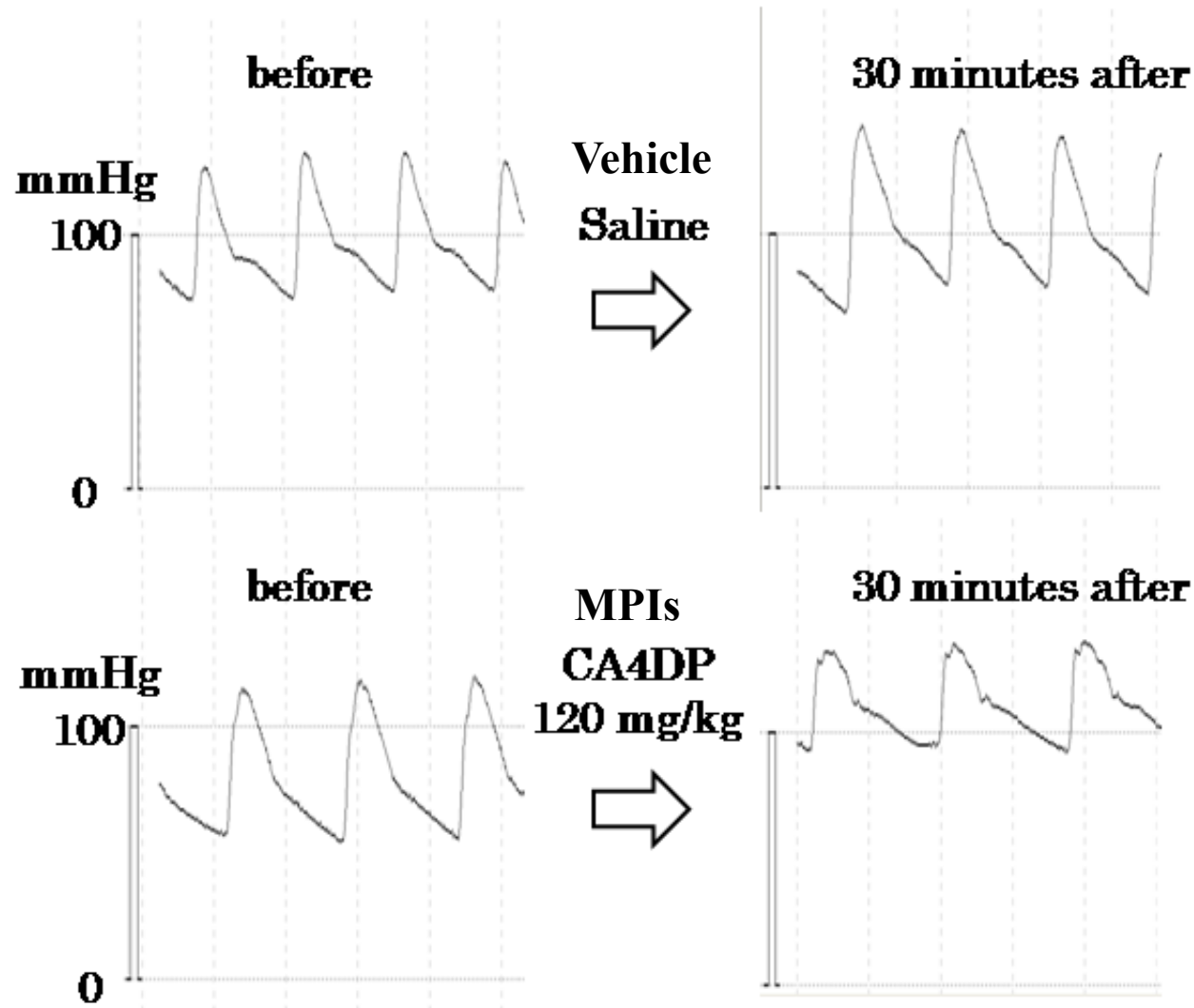
Beating rate

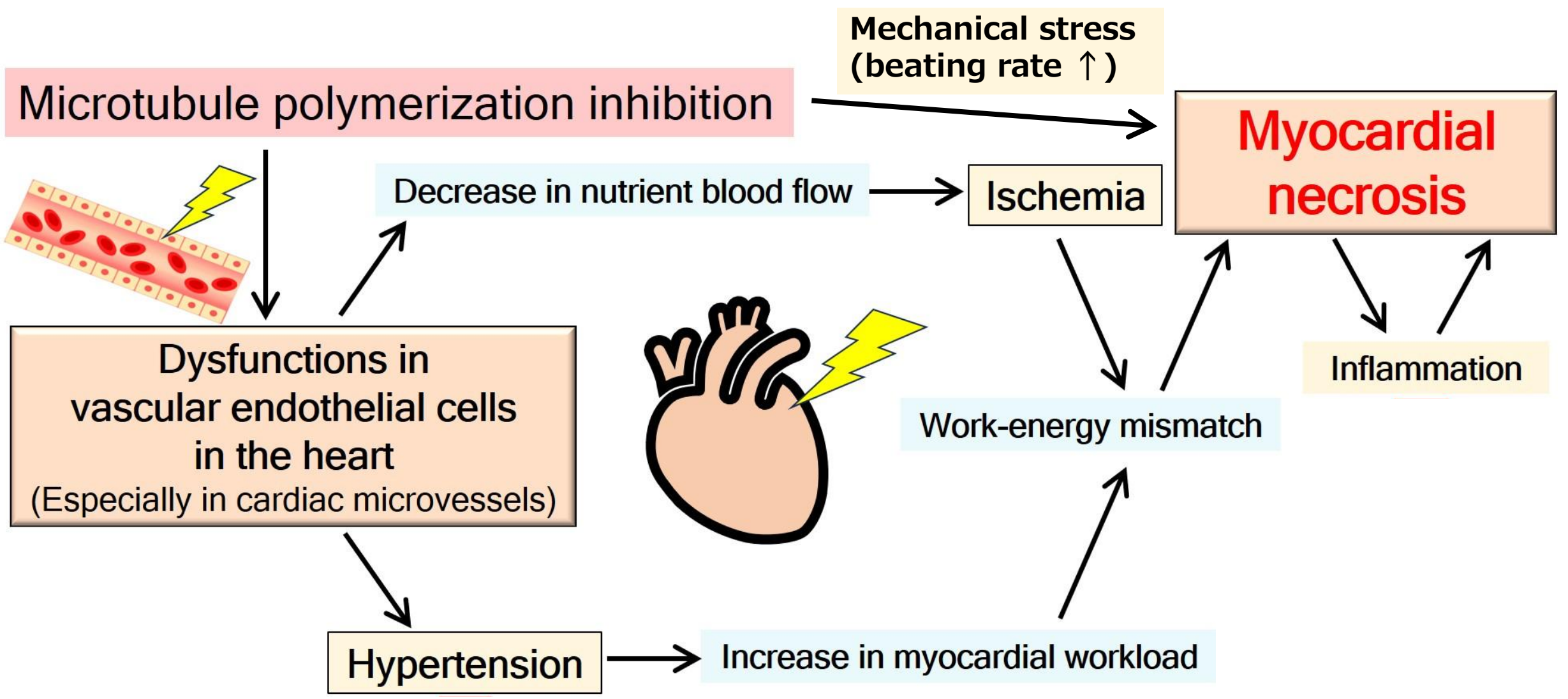


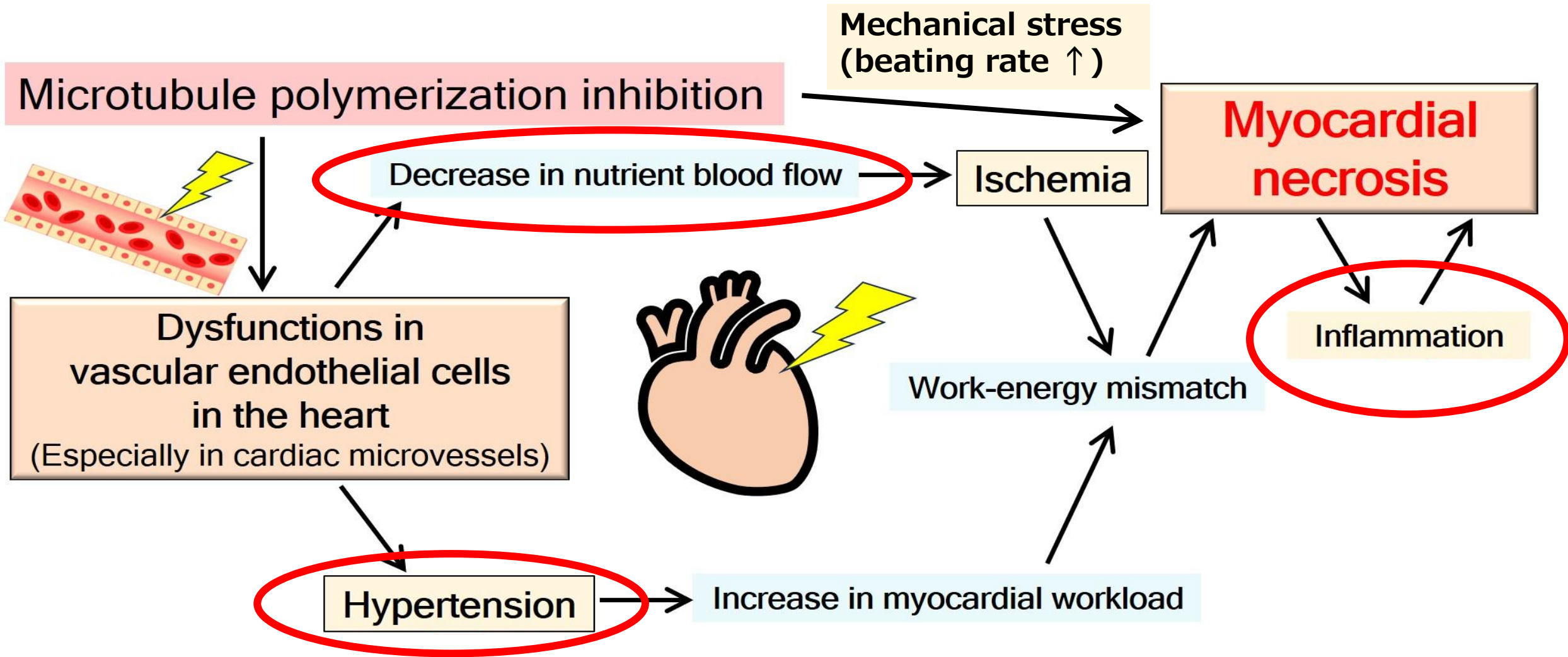
Tochinai R*, et al. J Toxicol Pathol. 2016.

MPIs induce hypertension

Blood pressure, femoral artery in rats.





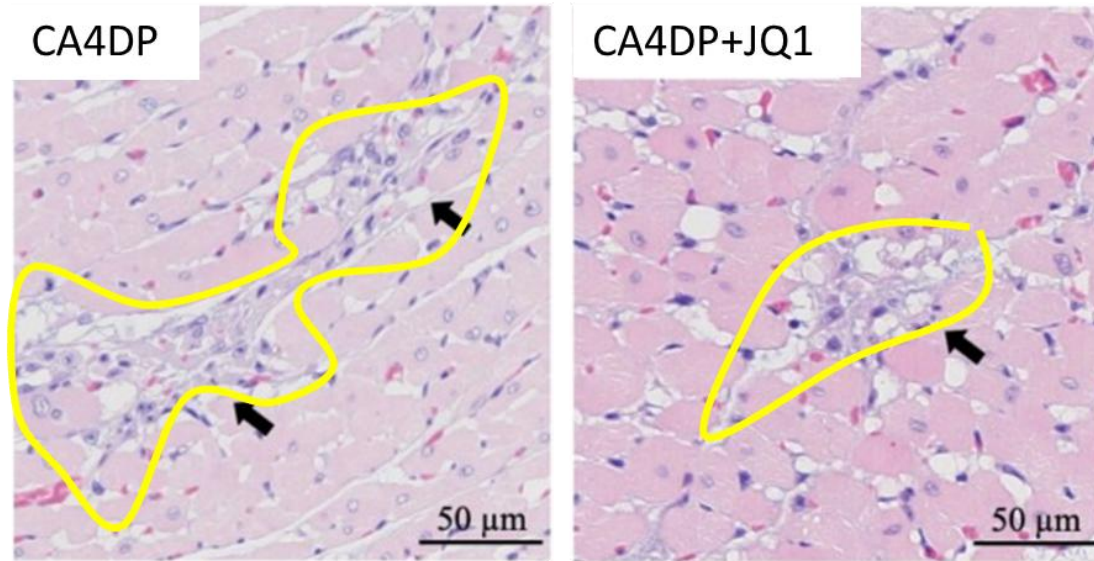


Tadalafil,
a phosphodiesterase (PDE) 5 inhibitor,
(vasodilator)

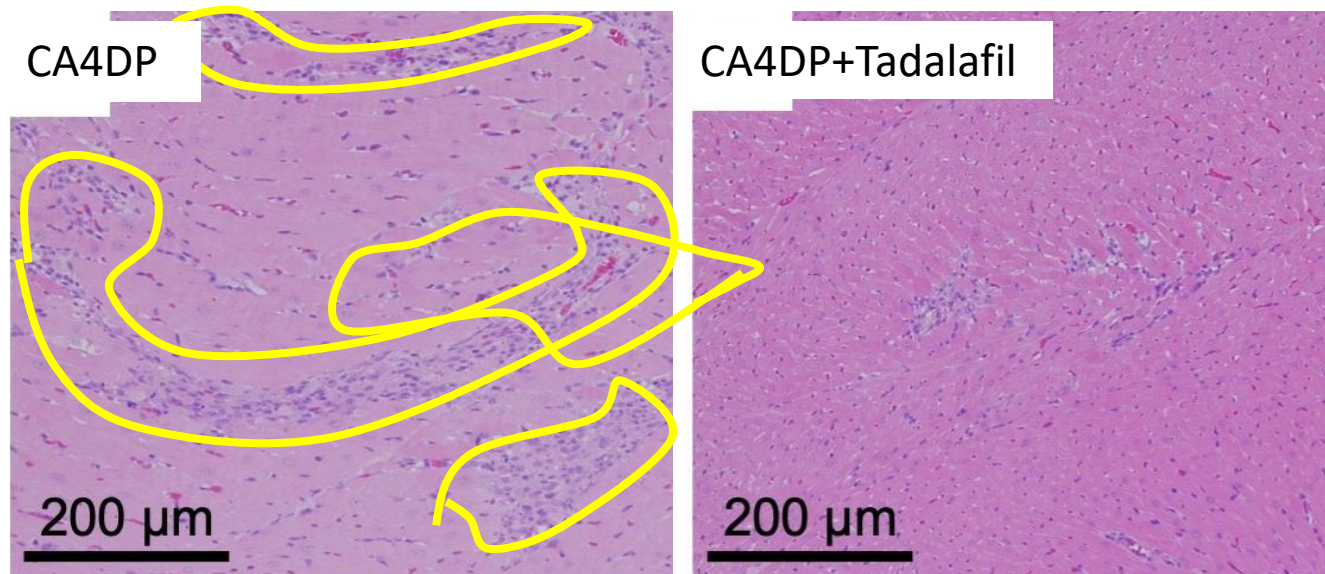
Could these drugs reduce the cardiotoxicity?

JQ-1,
a bromodomain-containing
protein 4 (BRD4) inhibitor,
(anti-inflammatory drug)

JQ-1 and Tadalafil can attenuate cardiac damage induced by MPIs

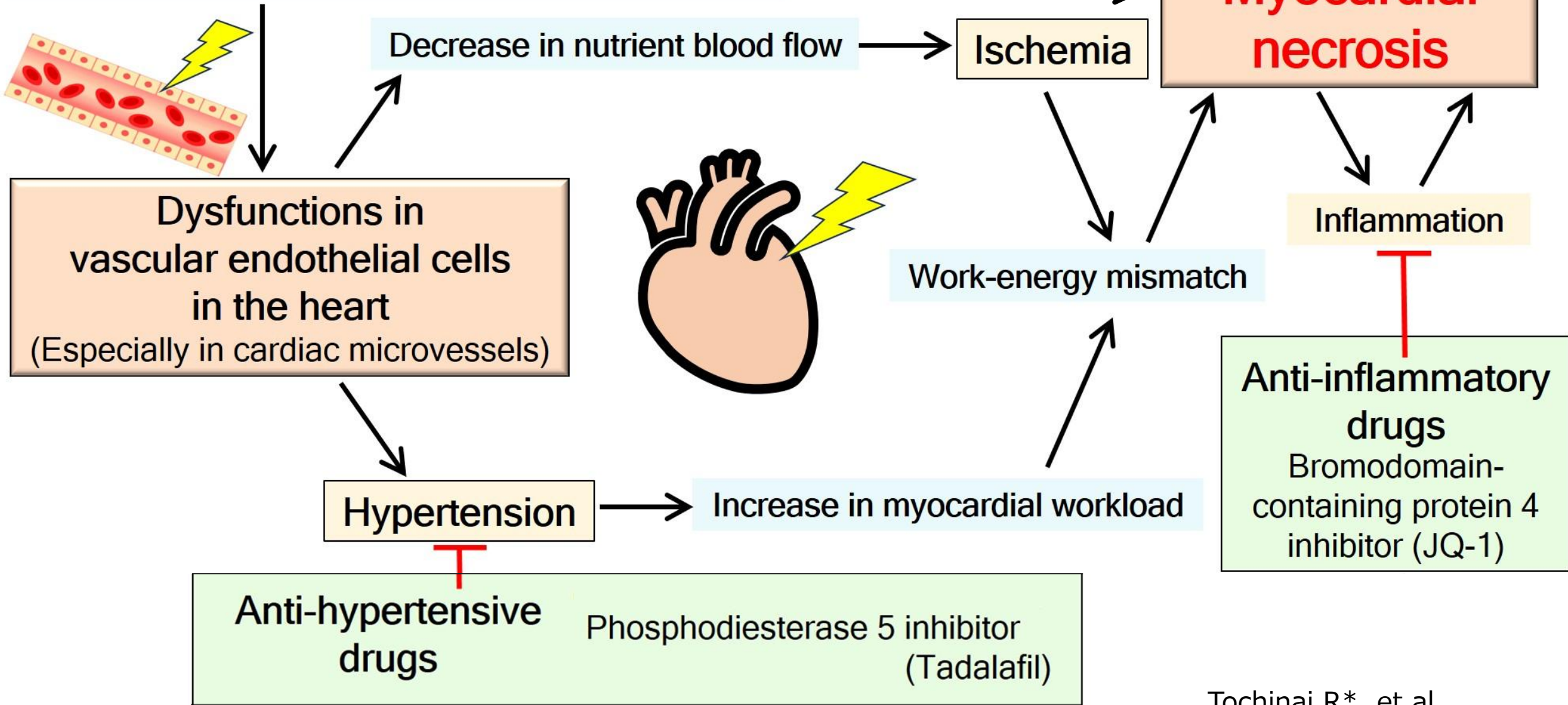


Orihara H, Ma M, Nagashima Y, Tochintai R*, et al.
Biomed Pharmacother, 2023



Nagashima Y, Tochintai R*, et al. J Toxicol Pathol. 2023

Microtubule polymerization inhibition



Tochinai R*, et al.
J. Appl. Toxicol. 2024.
modified

Acknowledgment

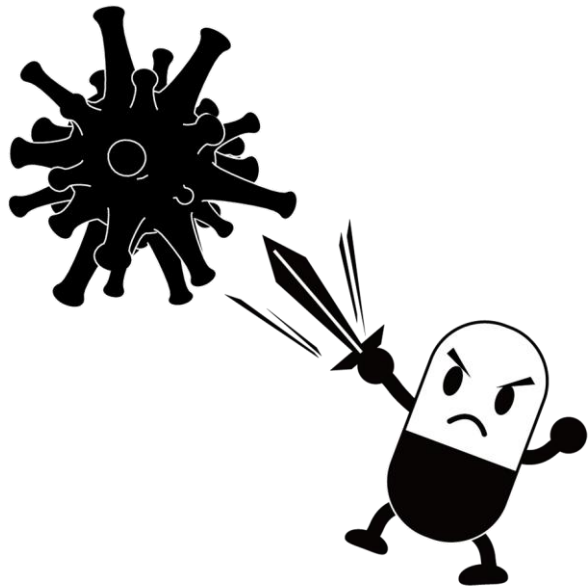
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Members of Lab. of Vet. Pathophysiol. and Anim. Health, UTokyo



Thank you for listening !

Let's work together to overcome the problems
that threaten living bodies,
such as cancer, infectious diseases, and beyond!!

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