

# [A 15-year study on up 4 a in cardiovascular disease](https://assignbuster.com/a-15-year-study-on-up-4-a-in-cardiovascular-disease/)

[](https://assignbuster.com/)[Health & Medicine](https://assignbuster.com/essay-subjects/health-n-medicine/)

## Introduction

In 2005, a novel dinucleotide uridine adenosine tetraphosphate (Up 4 A) was identified in the endothelium thereby being recognized as a novel endothelium-derived factor ( [Jankowski et al., 2005](#B3) ). Up 4 A is the first dinucleotide found in living organisms containing both a purine and a pyrimidine moieties ( [Jankowski et al., 2005](#B3) ). Up 4 A is biosynthesized through vascular endothelial growth factor receptor (VEGFR) 2 in response to pharmacological and mechanical stimuli ( [Jankowski et al., 2013](#B5) ). The plasma concentrations of Up 4 A in healthy subjects are in the vasoactive range suggesting that Up 4 A may contribute to cardiovascular regulation ( [Jankowski et al., 2005](#B3) ). Of importance, several pieces of evidence have reported that the plasma level of Up 4 A is elevated in patients with hypertension and with chronic kidney diseases, and that Up 4 A (via intra-aortic bolus injection) increases mean arterial pressure in rats *in vivo* ( [Jankowski et al., 2005](#B3) ; [Jankowski et al., 2007](#B4) ; [Schuchardt et al., 2012](#B14) ). These observations suggest a potential role for Up 4 A in the pathogenesis of cardiovascular disease.

During the following years, the research was focused on the vascular effect of Up 4 A in different vascular beds of various species. This mainly includes the acute effect of Up 4 A on vascular function in both health and various cardiovascular diseases including hypertension, atherosclerosis, myocardial infarction, and diabetes, and the trophic effect of Up 4 A on vascular proliferation, migration, angiogenesis, and calcification ( [Matsumoto et al., 2015](#B10) ; [Zhou et al., 2019](#B23) ). Up 4 A exerts biological effects by activating purinergic receptors (PRs) to regulate cardiovascular (dys)function. PRs are divided into P1R and P2R categories. Four subtypes of P1Rs (adenosine receptors) have been identified, namely A1R, A 2A R, A 2B R, and A3R. At least seven P2XRs, and eight P2YRs have been identified to date ( [Burnstock, 2017](#B1) ). In the vasculature, activation of A1R and A3R can induce contraction, whereas activation of A 2A R and A 2B R typically produce vascular relaxation ( [Zhou et al., 2019](#B23) ). In contrast to P1Rs, the effects of the activation of P2R subtypes may be tissue- and cell-dependent. In general, activation of P2R subtypes in endothelial cells are thought to induce vasodilation, while activation of P2Rs in smooth muscle cells can induce vasoconstriction ( [Zhou et al., 2019](#B23) ). Of note, the pharmacological action of Up 4 A on vascular function and the Up 4 A-mediated purinergic signaling have been shown to be altered in cardiovascular disease ( [Zhou et al., 2019](#B23) ). However, the endogenous role of Up 4 A in the regulation of cardiovascular homeostasis and particularly the role of Up 4 A in the development and progression of cardiovascular disease remain largely unclear. This study briefly summarizes the available information regarding the vascular action of Up 4 A and its mediated purinergic signaling in various cardiovascular diseases during a 15-year research period and raises critical questions and perspectives for the future research direction in order to better understand the biological role of Up 4 A in the development of cardiovascular disease.

## Up 4 A Biosynthesis and Catabolism

Up 4 A is biosynthesized by activation of VEGFR2 in the endothelium ( [Jankowski et al., 2013](#B5) ). After incubation of ADP and UDP with VEGFR2, human dermal endothelial cells generate increasing concentrations of Up 4 A, while there is no Up 4 A formation when incubating ADP and UDP with VEGFR1 or VEGFR3 ( [Jankowski et al., 2013](#B5) ). The domain of Tyr-1175 of VEGFR2 is essential for the enzymatic activity for Up 4 A synthesis ( [Jankowski et al., 2013](#B5) ). Up 4 A could facilitate VEGFR2-mediated signaling pathways e. g. p42/44 mitogen-activated protein kinase phosphorylation ( [Jankowski et al., 2013](#B5) ). Given that VEGFR2 is abundantly expressed in endothelial cells, the Up 4 A biosynthesis may play a significant role in cardiovascular homeostasis.

In addition to endothelial cells, Up 4 A was found to be generated in renal tubular cells, human liver hepatocellular carcinoma cells, human acute monocytic leukemia cells, and murine macrophage cells ( [Zhou et al., 2019](#B23) ). As these cells express VEGFR2, Up 4 A synthesis is likely also mediated by activation of VEGFR2. It is of interest to know whether VEGFR2-expressing cells are generally capable of synthesizing Up 4 A. Of further importance, several cardiovascular diseases including diabetes have demonstrated an altered VEGFR2 expression and function ( [Fountas et al., 2015](#B2) ). Whether such alteration may affect Up 4 A generation and subsequent purinergic activation accounting for the development and progression of disease remains unknown and warrants further studies.

Catabolism of Up 4 A is poorly understood. Dinucleotides can be degraded to mononucleotides by ecto-nucleotidases (including CD39 and CD37) ( [Burnstock, 2017](#B1) ). These ecto-nucleotidases are ubiquitously present in different cells, including vascular endothelial and smooth muscle cells ( [Burnstock, 2017](#B1) ). This implies that Up 4 A may be also degraded through those ecto-nucleotidases, and that the Up 4 A-mediated vascular effects can be exerted by its degradation products. However, existing evidence suggest that Up 4 A-mediated vascular effects are direct, but not indirect through its degradation or inhibition of purinergic enzymes as mentioned above ( [Zhou et al., 2019](#B23) ). It is speculated that the catabolism of Up 4 A may be through other types of ecto-nucleotidases e. g. nucleotide pyrophosphatase/phosphodiesterases. Further studies are needed to explore this mechanism. Of note, activity of these nucleotidases are altered in cardiovascular disease ( [Burnstock, 2017](#B1) ; [Zhou et al., 2020](#B24) ). It is of importance to know in the future studies whether altered nucleotidase activity may influence the catabolism of Up 4 A contributing to the initiation and/or development of cardiovascular disease.

## Up 4 A and Vascular Actions

Using pharmacological approach, the 15-year research on Up 4 A has unveiled vascular effects of Up 4 A in various cardiovascular diseases. The Up 4 A-mediated PR activation and possible downstream pathways have been characterized in hypertension, diabetes, atherosclerosis, and myocardial infarction. In addition, Up 4 A exerts various trophic effects through activation of P2YRs inducing angiogenesis in endothelial cells, proliferation and migration in smooth muscle cells, and development of calcification ( [Zhou et al., 2019](#B23) ). These chronic effects may also play a role for vascular remodeling and atherogenesis.

### Hypertension

Vascular reactivity to Up 4 A is altered in hypertension. In deoxycorticosterone acetate-salt rats, Up 4 A-induced contraction is heterogeneously affected among various vessels. Thus, Up 4 A-induced vascular contraction was increased in basilar, renal, and femoral arteries, but was decreased in small mesenteric arteries, and unchanged in thoracic aortas and pulmonary arteries ( [Matsumoto et al., 2011](#B7) ; [Matsumoto et al., 2012](#B8) ). Activation of P2YR contributed to the increased Up 4 A-induced contraction in basilar, femoral, and renal arteries ( [Matsumoto et al., 2011](#B7) ; [Matsumoto et al., 2012](#B8) ). In angiotensin II-induced hypertensive mice, Up 4 A-induced contraction in aortas was decreased likely due to P2X 1 R desensitization ( [Zhou et al., 2017b](#B20) ). These observations may imply that vascular PR activity rather than circulating Up 4 A may determine the role of Up 4 A in setting of hypertension. However, further investigations regarding the relationship between altered circulating Up 4 A and vascular PR activity in hypertension are needed. In contrast to vasoconstrictor effect, Up 4 A produces potent relaxation in porcine coronary small arteries ( [Zhou et al., 2013b](#B18) ; [Sun et al., 2019](#B15) ). In a swine model with pressure-overload-induced hypertension, Up 4 A-induced relaxation was impaired in coronary small arteries isolated from hypertensive swine compared to control. ARs other than A 2A R and P2Y 12 R among P2Rs are proposed contributing to the reduced relaxation to Up 4 A in hypertensive swine ( [Zhou et al., 2018a](#B21) ).

### Diabetes

Diabetes is an important risk factor for the development of cardiovascular diseases including atherosclerosis and ischemic heart disease ( [Pereira et al., 2018](#B13) ; [Zhou et al., 2018b](#B22) ). Diabetes-associated vascular complications are the leading causes of increased morbidity and mortality worldwide ( [Zhou et al., 2018b](#B22) ). Up 4 A-induced contraction in renal arteries of healthy rats, which was enhanced in vessels from Goto-Kakizaki (GK) rats likely due to activation of suramin-sensitive P2Rs ( [Matsumoto et al., 2014](#B9) ). Up 4 A-induced contraction was decreased in aortas and renal arteries of the Otsuka Long-Evans Tokushima Fatty (OLETF) diabetic rats as compared to control Long-Evans Tokushima Otsuka (LETO) rats at basal tone ( [Matsumoto et al., 2016](#B11) ; [Matsumoto et al., 2017](#B12) ). Of note, the Up 4 A-induced renal contraction in OLETF rats was increased with age and duration of diabetes, whereas the Up 4 A-induced contraction in LETO rats was not associated with age ( [Matsumoto et al., 2016](#B11) ). With elevated tone by phenylephrine, Up 4 A produced a mild relaxation in aortas isolated from OLETF rats as compared to the vasoconstrictor effect by Up 4 A in LETO rats ( [Matsumoto et al., 2017](#B12) ). The involvements of PRs in different vascular responses to Up 4 A in this model need further investigations. However, Up 4 A can stimulate other endothelium-derived factors e. g. vasoconstrictor prostanoids PGF 2α , PGE 2 , and thromboxane (TxA 2 ) are generated in response to Up 4 A to promote its contraction and nitric oxide is released to suppress Up 4 A effects in OLETF rats ( [Matsumoto et al., 2017](#B12) ). Interestingly, Up 4 A-induced relaxation in coronary small arteries was maintained in swine with diabetes and endothelial dysfunction compared to normal swine ( [Zhou et al., 2017a](#B19) ). This is due to a balanced purinergic activation (reduced vasodilator A 2A R and P2X 7 R vs. increased vasodilator P2Y 1 R) and endothelium-derived factor-mediated effects (vasodilator CYP 2C9 vs. vasoconstrictor CYP 2C9 and TxA2) in response to Up 4 A ( [Zhou et al., 2017a](#B19) ).

### Coronary Atherosclerosis and Myocardial Infarction

Plaque formation due to atherosclerosis in coronary vasculature is a major cause of ischemic heart disease. When the plaque ruptures, the ensuing thromboembolism may lead to ischemia and myocardial infarction ( [Marzilli et al., 2012](#B6) ). Despite all four ARs and many P2Rs are involved in the development of atherosclerosis and targeting P2Y 12 R is an effective strategy commonly used in patients with acute coronary syndrome ( [Burnstock, 2017](#B1) ), the experimental evidence for the involvement of PRs in coronary atherosclerosis is lacking. In coronary arteries isolated from *ApoE* knockout mice treated with a high fat diet, in which lesions were observed, P2X 1 R expression was decreased in endothelial cells, while P2X 1 R expression remained unaltered in smooth muscle cells. Hence, the smooth muscle to endothelial cell ratio of P2X 1 R was increased, suggesting a net vasoconstrictor effect of P2X 1 R in coronary atherosclerosis ( [Teng et al., 2017](#B16) ). Indeed, infusion of Up 4 A into isolated hearts from *ApoE* knockout mice with high fat diet decreased coronary flow more as compared to hearts from control mice through activation of vasoconstrictor P2X 1 R ( [Teng et al., 2017](#B16) ). In contrast to *ex vivo* experiments, a bolus *i. v.* injection of Up 4 A increased coronary blood flow to a similar extent between control and atherosclerotic mice ( [Teng et al., 2017](#B16) ). This vasodilator effect of Up 4 A is not influenced by the hemodynamic changes by the drug infusion. However, the possibility of a Up 4 A degradation to purine or adenosine to induce coronary vasodilation *in vivo* condition remain undetermined, which warrants further investigations. In swine after myocardial infarction, the sensitivity of the coronary small arteries to Up 4 A was reduced ( [Zhou et al., 2013a](#B17) ). The reduced vasodilator response to Up 4 A is due to a reduced contribution of P1R (A 2B R was proposed to be involved) ( [Zhou et al., 2013a](#B17) ).

## Conclusions and Perspective

The 15-year research on Up 4 A in cardiovascular system has yielded fruitful outcomes. Up 4 A produces both short-term and long-term vascular effects through both P1R and P2R. The Up 4 A-induced effects not only depend on various vascular beds but also different species. The involvement of PRs in response to Up 4 A is altered in various cardiovascular diseases. However, endogenous role of Up 4 A in the regulation of vascular function remains unclear. Although the vasoactive effect of Up 4 A may depend on receptor activity, the contribution of the Up 4 A plasma levels to vascular (dys)function in cardiovascular disease warrants further investigations. Future research directions need to focus on the following aspects to better understand the role of Up 4 A in the development and progression of cardiovascular disease: 1) Does the altered plasma levels of Up 4 A in cardiovascular disease merely serve as a diagnostic biomarker, and/or can endogenous Up 4 A (including local concentration of Up 4 A e. g. in coronary microcirculation) activate corresponding PRs serving as a causative factor? What are causal factors and mechanisms underlying regulation of local/circulating Up 4 A levels? 2) Given that Up 4 A can activate both P1Rs and P2Rs expressed in different cells of the cardiovascular system, it remains to be investigated which receptors play an essential role. 3) Can Up 4 A biosynthesis and its mediated main purinergic signaling be targeted for the treatment of cardiovascular disease? Whether targeting a single receptor or multiple receptors at the same time yields in the most effective therapeutic effects. 4) What are the mechanisms underlying the Up 4 A-mediated effect *in vivo* condition? 5) Can Up 4 A-mediated vascular effect be eventually translated into human situation? It may take many other 15 years to address all these important questions and concerns. However, the successful characterization of vascular effect of Up 4 A and PRs involved in cardiovascular disease mentioned in the present study have paved the way for the next research step.

## Dedication

This study is dedicated to the memory of Geoffrey Burnstock from Royal Free and University College Medical School, London, United Kingdom, who peacefully passed away on June 3 rd 2020.

## Author Contributions

ZZ conceived the study. ZZ and TM wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

## Funding

This work was supported by the Swedish Heart and Lung Foundation (20190341 to ZZ), the Loo and Hans Ostermans Foundation (2018-01213 and 2020-01209 to ZZ), and the Lars Hiertas Minne Foundation (FO2018-0156 to ZZ).

## Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

Burnstock, G. (2017). Purinergic Signaling in the Cardiovascular System. *Circ. Res.* 120 (1), 207–228. doi: 10. 1161/CIRCRESAHA. 116. 309726

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28057794/) | [CrossRef Full Text](https://doi.org/10.1161/CIRCRESAHA.116.309726) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=G.+Burnstock&publication_year=2017&title=Purinergic Signaling in the Cardiovascular System&journal=Circ.+Res.&volume=120&pages=207)

Fountas, A., Diamantopoulos, L. N., Tsatsoulis, A. (2015). Tyrosine Kinase Inhibitors and Diabetes: A Novel Treatment Paradigm? *Trends Endocrinol. Metab.* 26 (11), 643–656. doi: 10. 1016/j. tem. 2015. 09. 003

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26492832/) | [CrossRef Full Text](https://doi.org/10.1016/j.tem.2015.09.003) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+Fountas&author=L. N.+Diamantopoulos&author=A.+Tsatsoulis&publication_year=2015&title=Tyrosine Kinase Inhibitors and Diabetes%3A A Novel Treatment Paradigm&journal=Trends+Endocrinol.+Metab.&volume=26&pages=643)

Jankowski, V., Tolle, M., Vanholder, R., Schonfelder, G., van der Giet, M., Henning, L., et al. (2005). Uridine adenosine tetraphosphate: a novel endothelium- derived vasoconstrictive factor. *Nat. Med.* 11 (2), 223–227. doi: 10. 1038/nm1188

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/15665829/) | [CrossRef Full Text](https://doi.org/10.1038/nm1188) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=V.+Jankowski&author=M.+Tolle&author=R.+Vanholder&author=G.+Schonfelder&author=M.+van der Giet&author=L.+Henning&publication_year=2005&title=Uridine adenosine tetraphosphate%3A a novel endothelium- derived vasoconstrictive factor&journal=Nat.+Med.&volume=11&pages=223)

Jankowski, V., Meyer, A. A., Schlattmann, P., Gui, Y., Zheng, X. L., Stamcou, I., et al. (2007). Increased uridine adenosine tetraphosphate concentrations in plasma of juvenile hypertensives. *Arterioscler. Thromb. Vasc. Biol.* 27 (8), 1776–1781. doi: 10. 1161/ATVBAHA. 107. 143958

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/17569882/) | [CrossRef Full Text](https://doi.org/10.1161/ATVBAHA.107.143958) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=V.+Jankowski&author=A. A.+Meyer&author=P.+Schlattmann&author=Y.+Gui&author=X. L.+Zheng&author=I.+Stamcou&publication_year=2007&title=Increased uridine adenosine tetraphosphate concentrations in plasma of juvenile hypertensives&journal=Arterioscler.+Thromb.+Vasc.+Biol.&volume=27&pages=1776)

Jankowski, V., Schulz, A., Kretschmer, A., Mischak, H., Boehringer, F., van der Giet, M., et al. (2013). The enzymatic activity of the VEGFR2 receptor for the biosynthesis of dinucleoside polyphosphates. *J. Mol. Med. (Berl)* 91 (9), 1095–1107. doi: 10. 1007/s00109-013-1036-y

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/23636508/) | [CrossRef Full Text](https://doi.org/10.1007/s00109-013-1036-y) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=V.+Jankowski&author=A.+Schulz&author=A.+Kretschmer&author=H.+Mischak&author=F.+Boehringer&author=M.+van der Giet&publication_year=2013&title=The enzymatic activity of the VEGFR2 receptor for the biosynthesis of dinucleoside polyphosphates&journal=J.+Mol.+Med.+(Berl)&volume=91&pages=1095)

Marzilli, M., Merz, C. N., Boden, W. E., Bonow, R. O., Capozza, P. G., Chilian, W. M., et al. (2012). Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link! *J. Am. Coll. Cardiol.* 60 (11), 951–956. doi: 10. 1016/j. jacc. 2012. 02. 082

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/22954239/) | [CrossRef Full Text](https://doi.org/10.1016/j.jacc.2012.02.082) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Marzilli&author=C. N.+Merz&author=W. E.+Boden&author=R. O.+Bonow&author=P. G.+Capozza&author=W. M.+Chilian&publication_year=2012&title=Obstructive coronary atherosclerosis and ischemic heart disease%3A an elusive link&journal=J.+Am.+Coll.+Cardiol.&volume=60&pages=951)

Matsumoto, T., Tostes, R. C., Webb, R. C. (2011). Uridine adenosine tetraphosphate-induced contraction is increased in renal but not pulmonary arteries from DOCA-salt hypertensive rats. *Am. J. Physiol. Heart Circ. Physiol.* 301 (2), H409–H417. doi: 10. 1152/ajpheart. 00084. 2011

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/21551273/) | [CrossRef Full Text](https://doi.org/10.1152/ajpheart.00084.2011) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=T.+Matsumoto&author=R. C.+Tostes&author=R. C.+Webb&publication_year=2011&title=Uridine adenosine tetraphosphate-induced contraction is increased in renal but not pulmonary arteries from DOCA-salt hypertensive rats&journal=Am.+J.+Physiol.+Heart+Circ.+Physiol.&volume=301&pages=H409)

Matsumoto, T., Tostes, R. C., Webb, R. C. (2012). Alterations in vasoconstrictor responses to the endothelium-derived contracting factor uridine adenosine tetraphosphate are region specific in DOCA-salt hypertensive rats. *Pharmacol. Res.* 65 (1), 81–90. doi: 10. 1016/j. phrs. 2011. 09. 005

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/21933714/) | [CrossRef Full Text](https://doi.org/10.1016/j.phrs.2011.09.005) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=T.+Matsumoto&author=R. C.+Tostes&author=R. C.+Webb&publication_year=2012&title=Alterations in vasoconstrictor responses to the endothelium-derived contracting factor uridine adenosine tetraphosphate are region specific in DOCA-salt hypertensive rats&journal=Pharmacol.+Res.&volume=65&pages=81)

Matsumoto, T., Watanabe, S., Kawamura, R., Taguchi, K., Kobayashi, T. (2014). Enhanced uridine adenosine tetraphosphate-induced contraction in renal artery from type 2 diabetic Goto-Kakizaki rats due to activated cyclooxygenase/thromboxane receptor axis. *Pflugers Arch.* 466 (2), 331–342. doi: 10. 1007/s00424-013-1330-0

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/23900807/) | [CrossRef Full Text](https://doi.org/10.1007/s00424-013-1330-0) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=T.+Matsumoto&author=S.+Watanabe&author=R.+Kawamura&author=K.+Taguchi&author=T.+Kobayashi&publication_year=2014&title=Enhanced uridine adenosine tetraphosphate-induced contraction in renal artery from type 2 diabetic Goto-Kakizaki rats due to activated cyclooxygenase%2Fthromboxane receptor axis&journal=Pflugers+Arch.&volume=466&pages=331)

Matsumoto, T., Goulopoulou, S., Taguchi, K., Tostes, R. C., Kobayashi, T. (2015). Constrictor prostanoids and uridine adenosine tetraphosphate: vascular mediators and therapeutic targets in hypertension and diabetes. *Br. J. Pharmacol.* 172 (16), 3980–4001. doi: 10. 1111/bph. 13205

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26031319/) | [CrossRef Full Text](https://doi.org/10.1111/bph.13205) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=T.+Matsumoto&author=S.+Goulopoulou&author=K.+Taguchi&author=R. C.+Tostes&author=T.+Kobayashi&publication_year=2015&title=Constrictor prostanoids and uridine adenosine tetraphosphate%3A vascular mediators and therapeutic targets in hypertension and diabetes&journal=Br.+J.+Pharmacol.&volume=172&pages=3980)

Matsumoto, T., Watanabe, S., Ando, M., Yamada, K., Iguchi, M., Taguchi, K., et al. (2016). Diabetes and Age-Related Differences in Vascular Function of Renal Artery: Possible Involvement of Endoplasmic Reticulum Stress. *Rejuvenation Res.* 19 (1), 41–52. doi: 10. 1089/rej. 2015. 1662

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26234558/) | [CrossRef Full Text](https://doi.org/10.1089/rej.2015.1662) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=T.+Matsumoto&author=S.+Watanabe&author=M.+Ando&author=K.+Yamada&author=M.+Iguchi&author=K.+Taguchi&publication_year=2016&title=Diabetes and Age-Related Differences in Vascular Function of Renal Artery%3A Possible Involvement of Endoplasmic Reticulum Stress&journal=Rejuvenation+Res.&volume=19&pages=41)

Matsumoto, T., Kobayashi, S., Ando, M., Iguchi, M., Takayanagi, K., Kojima, M., et al. (2017). Alteration of Vascular Responsiveness to Uridine Adenosine Tetraphosphate in Aortas Isolated from Male Diabetic Otsuka Long-Evans Tokushima Fatty Rats: The Involvement of Prostanoids. *Int. J. Mol. Sci.* 18 (11), 2378. doi: 10. 3390/ijms18112378

[CrossRef Full Text](https://doi.org/10.3390/ijms18112378) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=T.+Matsumoto&author=S.+Kobayashi&author=M.+Ando&author=M.+Iguchi&author=K.+Takayanagi&author=M.+Kojima&publication_year=2017&title=Alteration of Vascular Responsiveness to Uridine Adenosine Tetraphosphate in Aortas Isolated from Male Diabetic Otsuka Long-Evans Tokushima Fatty Rats%3A The Involvement of Prostanoids&journal=Int.+J.+Mol.+Sci.&volume=18&pages=2378)

Pereira, C. A., Carneiro, F. S., Matsumoto, T., Tostes, R. C. (2018). Bonus Effects of Antidiabetic Drugs: Possible Beneficial Effects on Endothelial Dysfunction, Vascular Inflammation and Atherosclerosis. *Basic Clin. Pharmacol. Toxicol.* 123 (5), 523–538. doi: 10. 1111/bcpt. 13054

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/29890033/) | [CrossRef Full Text](https://doi.org/10.1111/bcpt.13054) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=C. A.+Pereira&author=F. S.+Carneiro&author=T.+Matsumoto&author=R. C.+Tostes&publication_year=2018&title=Bonus Effects of Antidiabetic Drugs%3A Possible Beneficial Effects on Endothelial Dysfunction%2C Vascular Inflammation and Atherosclerosis&journal=Basic+Clin.+Pharmacol.+Toxicol.&volume=123&pages=523)

Schuchardt, M., Tolle, M., Prufer, J., Prufer, N., Huang, T., Jankowski, V., et al. (2012). Uridine adenosine tetraphosphate activation of the purinergic receptor P2Y enhances in vitro vascular calcification. *Kidney Int.* 81 (3), 256–265. doi: 10. 1038/ki. 2011. 326

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/21956191/) | [CrossRef Full Text](https://doi.org/10.1038/ki.2011.326) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Schuchardt&author=M.+Tolle&author=J.+Prufer&author=N.+Prufer&author=T.+Huang&author=V.+Jankowski&publication_year=2012&title=Uridine adenosine tetraphosphate activation of the purinergic receptor P2Y enhances in vitro vascular calcification&journal=Kidney+Int.&volume=81&pages=256)

Sun, C., Jiao, T., Merkus, D., Duncker, D. J., Mustafa, S. J., Zhou, Z. (2019). Activation of adenosine A2A but not A2B receptors is involved in uridine adenosine tetraphosphate-induced porcine coronary smooth muscle relaxation. *J. Pharmacol. Sci.* 141 (1), 64–69. doi: 10. 1016/j. jphs. 2019. 09. 006

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/31640919/) | [CrossRef Full Text](https://doi.org/10.1016/j.jphs.2019.09.006) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=C.+Sun&author=T.+Jiao&author=D.+Merkus&author=D. J.+Duncker&author=S. J.+Mustafa&author=Z.+Zhou&publication_year=2019&title=Activation of adenosine A2A but not A2B receptors is involved in uridine adenosine tetraphosphate-induced porcine coronary smooth muscle relaxation&journal=J.+Pharmacol.+Sci.&volume=141&pages=64)

Teng, B., Labazi, H., Sun, C., Yang, Y., Zeng, X., Mustafa, S. J., et al. (2017). Divergent coronary flow responses to uridine adenosine tetraphosphate in atherosclerotic ApoE knockout mice. *Purinergic Signal* 13 (4), 591–600. doi: 10. 1007/s11302-017-9586-z

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28929376/) | [CrossRef Full Text](https://doi.org/10.1007/s11302-017-9586-z) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=B.+Teng&author=H.+Labazi&author=C.+Sun&author=Y.+Yang&author=X.+Zeng&author=S. J.+Mustafa&publication_year=2017&title=Divergent coronary flow responses to uridine adenosine tetraphosphate in atherosclerotic ApoE knockout mice&journal=Purinergic+Signal&volume=13&pages=591)

Zhou, Z., de Wijs-Meijler, D., Lankhuizen, I., Jankowski, J., Jankowski, V., Jan Danser, A. H., et al. (2013a). Blunted coronary vasodilator response to uridine adenosine tetraphosphate in post-infarct remodeled myocardium is due to reduced P1 receptor activation. *Pharmacol. Res.* 77, 22–29. doi: 10. 1016/j. phrs. 2013. 08. 007

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/23994209/) | [CrossRef Full Text](https://doi.org/10.1016/j.phrs.2013.08.007) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Z.+Zhou&author=D.+de Wijs-Meijler&author=I.+Lankhuizen&author=J.+Jankowski&author=V.+Jankowski&author=A. H.+Jan Danser&publication_year=2013&title=Blunted coronary vasodilator response to uridine adenosine tetraphosphate in post-infarct remodeled myocardium is due to reduced P1 receptor activation&journal=Pharmacol.+Res.&volume=77&pages=22)

Zhou, Z., Merkus, D., Cheng, C., Duckers, H. J., Jan Danser, A. H., Duncker, D. J. (2013b). Uridine adenosine tetraphosphate is a novel vasodilator in the coronary microcirculation which acts through purinergic P1 but not P2 receptors. *Pharmacol. Res.* 67 (1), 10–17. doi: 10. 1016/j. phrs. 2012. 09. 011

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/23063485/) | [CrossRef Full Text](https://doi.org/10.1016/j.phrs.2012.09.011) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Z.+Zhou&author=D.+Merkus&author=C.+Cheng&author=H. J.+Duckers&author=A. H.+Jan Danser&author=D. J.+Duncker&publication_year=2013&title=Uridine adenosine tetraphosphate is a novel vasodilator in the coronary microcirculation which acts through purinergic P1 but not P2 receptors&journal=Pharmacol.+Res.&volume=67&pages=10)

Zhou, Z., Sorop, O., de Beer, V. J., Heinonen, I., Cheng, C., Jan Danser, A. H., et al. (2017a). Altered purinergic signaling in uridine adenosine tetraphosphate-induced coronary relaxation in swine with metabolic derangement. *Purinergic Signal* 13 (3), 319–329. doi: 10. 1007/s11302-017-9563-6

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28540569/) | [CrossRef Full Text](https://doi.org/10.1007/s11302-017-9563-6) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Z.+Zhou&author=O.+Sorop&author=V. J.+de Beer&author=I.+Heinonen&author=C.+Cheng&author=A. H.+Jan Danser&publication_year=2017&title=Altered purinergic signaling in uridine adenosine tetraphosphate-induced coronary relaxation in swine with metabolic derangement&journal=Purinergic+Signal&volume=13&pages=319)

Zhou, Z., Yadav, V. R., Sun, C., Teng, B., Mustafa, J. S. (2017b). Impaired Aortic Contractility to Uridine Adenosine Tetraphosphate in Angiotensin II-Induced Hypertensive Mice: Receptor Desensitization? *Am. J. Hypertens.* 30 (3), 304–312. doi: 10. 1093/ajh/hpw163

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28034895/) | [CrossRef Full Text](https://doi.org/10.1093/ajh/hpw163) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Z.+Zhou&author=V. R.+Yadav&author=C.+Sun&author=B.+Teng&author=J. S.+Mustafa&publication_year=2017&title=Impaired Aortic Contractility to Uridine Adenosine Tetraphosphate in Angiotensin II-Induced Hypertensive Mice%3A Receptor Desensitization&journal=Am.+J.+Hypertens.&volume=30&pages=304)

Zhou, Z., Lankhuizen, I. M., van Beusekom, H. M., Cheng, C., Duncker, D. J., Merkus, D. (2018a). Uridine Adenosine Tetraphosphate-Induced Coronary Relaxation Is Blunted in Swine With Pressure Overload: A Role for Vasoconstrictor Prostanoids. *Front. Pharmacol.* 9, 255. doi: 10. 3389/fphar. 2018. 00255

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/29632487/) | [CrossRef Full Text](https://doi.org/10.3389/fphar.2018.00255) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Z.+Zhou&author=I. M.+Lankhuizen&author=H. M.+van Beusekom&author=C.+Cheng&author=D. J.+Duncker&author=D.+Merkus&publication_year=2018&title=Uridine Adenosine Tetraphosphate-Induced Coronary Relaxation Is Blunted in Swine With Pressure Overload%3A A Role for Vasoconstrictor Prostanoids&journal=Front.+Pharmacol.&volume=9&)

Zhou, Z., Mahdi, A., Tratsiakovich, Y., Zahoran, S., Kovamees, O., Nordin, F., et al. (2018b). Erythrocytes From Patients With Type 2 Diabetes Induce Endothelial Dysfunction Via Arginase I. *J. Am. Coll. Cardiol.* 72 (7), 769–780. doi: 10. 1016/j. jacc. 2018. 05. 052

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/30092954/) | [CrossRef Full Text](https://doi.org/10.1016/j.jacc.2018.05.052) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Z.+Zhou&author=A.+Mahdi&author=Y.+Tratsiakovich&author=S.+Zahoran&author=O.+Kovamees&author=F.+Nordin&publication_year=2018&title=Erythrocytes From Patients With Type 2 Diabetes Induce Endothelial Dysfunction Via Arginase I&journal=J.+Am.+Coll.+Cardiol.&volume=72&pages=769)

Zhou, Z., Matsumoto, T., Jankowski, V., Pernow, J., Mustafa, S. J., Duncker, D. J., et al. (2019). Uridine adenosine tetraphosphate and purinergic signaling in cardiovascular system: An update. *Pharmacol. Res.* 141, 32–45. doi: 10. 1016/j. phrs. 2018. 12. 009

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/30553823/) | [CrossRef Full Text](https://doi.org/10.1016/j.phrs.2018.12.009) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Z.+Zhou&author=T.+Matsumoto&author=V.+Jankowski&author=J.+Pernow&author=S. J.+Mustafa&author=D. J.+Duncker&publication_year=2019&title=Uridine adenosine tetraphosphate and purinergic signaling in cardiovascular system%3A An update&journal=Pharmacol.+Res.&volume=141&pages=32)

Zhou, R., Dang, X., Sprague, R. S., Mustafa, S. J., Zhou, Z. (2020). Alteration of purinergic signaling in diabetes: Focus on vascular function. *J. Mol. Cell Cardiol.* 140, 1–9. doi: 10. 1016/j. yjmcc. 2020. 02. 004

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/32057736/) | [CrossRef Full Text](https://doi.org/10.1016/j.yjmcc.2020.02.004) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=R.+Zhou&author=X.+Dang&author=R. S.+Sprague&author=S. J.+Mustafa&author=Z.+Zhou&publication_year=2020&title=Alteration of purinergic signaling in diabetes%3A Focus on vascular function&journal=J.+Mol.+Cell+Cardiol.&volume=140&pages=1)