Nitric oxide (NO) is an important organizer of the cardiovascular function and is an important mechanism in maintaining cardiovascular functions in humans [1–5]. The NO that argues positions in the myocardium can be obtained via exogenous matters or is generated from the endogenous NO synthases and alertable NO by inflammatory cytokines following infection [4–6]. The impacts of NO on myocardial functions and the roles for NOS in diseased hearts has improved in the last times. Overall approaches have been assumed to succeed this outcome, containing manipulation of stabilizers of to supplementation of NO mimetics, and the practical arguments of NO and its regulators in therapeutic approaches of post-transcriptional modifications which are soluble guanylate cyclase (sGC)/cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG)-dependent phosphorylation, S-nitrosylation, and trans-nitrosylation. 4) the downgradient stabilizers of NO differ from proteins and enzymes in the mitochondria and membrane. 5) NOS generates several radicals in addition to that NO (varied NO-associated yields) and maintains NO in the myocardium. Recent consensus indicates the importance of nNOS protein in cardiac protection under pathological stress and NO-dependent mechanisms are better understood in healthy and diseased hearts.

Resource of NO and effect mechanisms

It is affirmed that NO is varied from the standard L-arginine→NOS→NO way. Actually, NO that performs functions in the myocardium may also be obtained from the other source of NO. Nitrate (NO3−) in many types of green vegetables [9–11], is taken up into the plasma to become a safe reservoir and the active site of NO production. NO from this source is taken on by the salivary, is secreted in the intensified form in the saliva, and is right after diminished to more active nitrite (NO2−) in the oral cavity by nitrate reductases of commensal bacteria. Nitrate is decreased to NO in the stomach and is sucked up into the plasma in the gastrointestinal system. Many proteins are known to be contained in the NO metabolite cycle and nitrate’s reduction to NO, including xanthine oxidase [12,13], deoxyhemoglobin and deoxymyoglobin [14–16], neuroglobin [17], respiratory chain enzymes [18], cytochrome P450 [19], aldehyde oxidase [20], carbonic anhydrase (21) and NO synthase [22,23]. In-depth, up to 25% of nitrate re-uptake by the salivary and generates NO in the circulation; the rest of the nitrate is secreted in the urine. The number of NO from exogenous can be as high as the number that is generated from NOS in the tissues, indicating the importance of this pathway in supplementing local NO in the tissue. The effectiveness, food derived functional NO is oxygen independent [10,11]. Accordingly, NO from this source becomes more important in ischemic conditions, like myocardial infarction. NO can undergo an oxidative process via nNOS and generate nitrate, which can be diminished back to nitrite and NO by nitrate reductases, such as xanthine oxidoreductase or aldehyde oxidase [10,11]. Consequently, there is a fixed of NO metabolites, and NO that maintains exogenous NO in the body. The respective additives of the endogenous versus exogenous NO to intracellular signaling and function in hearts in vivo remain to reveal. Some tissues are the active sites for NO production from constitutive NOS. Lately, it has demonstrated that muscle is a nitrate store up that gains plasma NO because of the wide surface area in the body [24]. nNOS in the skeletal muscle promotes to the supply because it is the isofor in the skeletal muscle [25]. But, the NO from the specific sources that promote to the bioavailable NO in the myocardium. eNOS is the main isofor of NOS that plays significant roles in NO regulation of functions in the majority of tissues, including the heart [4,5,7,8].
bioavailability is limited in an oxidative and nitrosative stress environment, such as during ischemia reperfusion. S-nitrosylation can be ceased by the action of nitrosylates, with NADH and NADPH serving as electron donors to regenerate glutathione and thioredoxin. Many types of proteins are targeted by NO e.g., inhibition of protein phosphatase 2A/protein phosphatase one by NO causes protein kinase A (PKA) and phospholamban (PLN) [46], while NO activation by NO in the myocardium of rats [32]. Contrary, phosphodiesterase 5 (PDE5) reactivation by NO system limits cytosolic cGMP, a negative feedback mechanism of NO regulation of cGMP in cardiac myocytes [47]. Additionally, by targeting cardiac oxidases, such as xanthine oxidoreductase [48], NADPH oxidase [49,50], and mitochondrial reactive oxygen species (ROS) production [51], nNOS-derived from NO controls in the myocardium. Cysteine residues are the targets of ROS to cause S-glutathionylation in the proteins [52,53]; thus, S-nitrosylation by NO may block cysteine residues from irreversible oxidation under the conditions. Eventually, post-transcriptional terms downstream of NO change the proteins, altering their activity, and function, as well as, nNOS has been showed to generate H2O2 in the endothelium of arteries, for example, the aorta, and H2O2 mediates endothelium-dependent vascular relaxation [54,55]. Contrary, blight of endothelial has been demonstrated to worsen endothelial function in some diseases [56–58], likewise, both eNOS and nNOS promote to acetylcholine stimulation of vasodilation [55], by regulating protein kinases and phosphatases [59–61]. Conversely, uncoupling of eNOS and nNOS [48,62–64], results in the production of superoxide (O2•−) in return for NO; eNOS and nNOS occur the oxidative stress for pathological progression in the heart. nNOS performs its cardiac protection via the ion channels, modulating abnormal Ca2+ homeostasis, and mitochondrial function for the pathological process [7,8]. nNOS organizes ion channels and Ca2+-handling proteins. Specially, nNOS has permanently been demonstrated to diminish Ca2+ influx via the L-type Ca2+ channel (LTCC) [65]. In support of this, nNOS enhances the vulnerability of the LTCC for Ca2+-dependent inactivation in hypertension [66] where intracellular Ca2+ transient is increased secondary to NO-dependent myofilament Ca2+ desensitization (34). Variation of the LTCC by nNOS may prohibit extreme intracellular Ca2+ in myocytes under pathological situations. The ryanodine receptor (RyR) by nNOS has been contained in diminishing diastolic Ca2+ leak [67], increasing RyR open probability, and growing contraction in cardiac myocytes [74]. Thus, nNOS protects against arrhythmogenesis by modulating Ca2+ transients [68–70]. Besides, nNOS activity at the plasma membrane causes more significant Na+ influx via voltage-gated sodium channels via S-nitrosylation and increases the susceptibility of the myocardin for long QT and arrhythmias (34). Potassium channels are also potential targets of nNOS through S-nitrosylation and/or cGMP/PKG-dependent phosphorylation [71–73], which may play significant roles in the formation of cardiac function in hearts. NNOS-derived NO can cause S-nitrosylation of the SR calcium ATPase (SERCA) both under basal conditions [70,74]. Inhibition of nNOS decreases S-nitrosylation of SERCA at baseline level, and this is related to reduced Ca2+ uptake in the SR and decreased relaxation [74].
But, the functional important of this formation under disease situations survives to be detected. These results consider that the modes of post-transcriptional modification that underlie the specific impacts of nNOS are excessively dynamic, and this may optimize its formation of the target proteins under many stimuli, containing pressure overload.

A recent study has demonstrated that nNOS enhances cGMP/PKG-dependent phosphorylation of cardiac troponin I and cardiac myosin binding protein C and contributes myocyte relaxation in hypertension via cGMP/PKG-dependent myofilament Ca2+ desensitization (30) (Figure 1). Myofilament proteins are the targets of nNOS that mediate relaxation in cardiac myocytes to decrease the myocardium in hypertensive heart. Exogenous NO donors ease myocardial relaxation through sGC and cGMP/PKG-dependent phosphorylation of cTnl and myofilament Ca2+ desensitization [75]. A recent report has shown that NO mimetics diminish myofilament Ca2+ sensitivity and contractility by causing the S-nitrosylation of many myofilament proteins containing actin, myosin, and troponin C (cTnC) [76]. These results suggest that phosphorylation and the myofilament proteins are the fundamental mechanisms that mediate the effects of nNOS in the heart. nNOS is considered as the isoform that is stated in the mitochondria to organize cardiac metabolism [76]. NO inhibits cytochrome c oxidase activity by competing with O2 and inhibits electron transfer of complex III or NADH-dehydrogenase function at the level of complex I and enhances mitochondrial formation of O2−. Eventually, NO inhibits the mitochondrial respiration chain and diminish mitochondrial oxygen consumption [77-83]. In this respect, NO has been approved as a regulator of mitochondrial activity and metabolism. Even so, conditional overexpression of nNOS in the myocardium has related to enhanced nNOS in the mitochondria and a reduction in oxidative stress following myocardial infarction [51]. The modulation of oxidative stress by endogenous nNOS in diseased hearts can be a protective mechanism. Emerging evidence demonstrates that nNOS-derived NO plays leading roles in mitochondrial biogenesis [84,85], to maintain or enhance mitochondrial integrity and activity. For example, nNOS has been shown to be distributed to the nucleus through α-syntrophin via its PDZ domain in a variety of cells, containing myocytes [33,86]. Enhanced S-nitrosylation of nuclear proteins, containing cAMP response element-binding protein (CREB), in interacts with the promoter of the gene encoding peroxisome proliferator-activated receptor γ coactivator (PGC)-1α promoter, a central component of biogenesis and nuclear respiratory factor 1 [33]. NO has also included in cardiac energetics by impressing carbohydrate metabolism of mitochondria (Figure 2).

**Clinical usage**

Nitroglycerin has been used clinically in the treatment of CVD for more than 150 years. Enhanced acknowledgment of the mechanistic insights into NO signaling, the decomposition of NO, and the properties of NOs modern technology allows different attitudes to enhance NO bioavailability in tissues for the desired responses as well. In principle, enhancement of NO and its signaling can be succeeded via three ways: enhance sources to contribute NO production, reduce NO metabolism/degradation, and stimulate downstream signaling of NO. Delivering nitrate and nitrite to step up systemic or local NO via nitrate–nitrite–NO and the nitrate–nitrite–NO–fatty acid pathways are arguably the most active area under investigation experimentally and in the clinic [10]. So far, some putative precursors of NO have been described and are developing. Dietary consumption of NO precursors is an efficient way of nitrate delivery; programming of a suitable diet regime for vulnerable populations will be necessary to diminish the cardiovascular risks the economic burden on national healthcare systems as well. The correlation between the daily consumption of nitrate and cardiovascular events is notable. For instance, high vegetable units received in Japanese historically recognised have low rates of CVD is related to greater circulating nitrate and nitrite [87], contrasted to those in the western world, where average daily nitrate intake ranges from 40–100 mg and 30–180 mg, respectively, and the rates of CVD are high [88,89]. Moreover, the use of “healthy” fats, as in the Mediterranean diet, in the form of unsaturated fatty acids, is useful in preventing the development of CVD and decreases the risk factors [90]. Especially, nitrite reduction to NO happens in the presence of hypoxia and acidosis, during physical exercise, at the time when the cardiac muscle needs NO. In rotation, supplementation of NO substrates, e.g. arginine, L-citrulline, and BH4, and inhibition of arginase and

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NO and NOS that are feasible for CVD and therapeutic pathway exert high cardiovascular protection; but, research of consequences. By and large, NO and its downstream signaling cascades that lead to different physiological and pathological trans-nitrosylation) and the numbers and types of effectors cGMP/PKG-dependent phosphorylation, S-nitrosylation, and through the entire salivary NO pathway and from NOSs as well NO precursors, nitrate from skeletal muscles, NO production by regulation mechanisms containing daily consumption of NO in the myocardium, and effectiveness of NO is con...myocardium should be considered. Stimulation of the downstream signaling pathway of NO is a recovered strategy to target the effector proteins. The oral sGC stimulators, and atrial, brain, and C-type natriuretic peptides are in using to enhance cellular Cgmp [11]. Inhibition of a negative regulator of cGMP, PDE5 is another therapeutic approach to stimulate cGMP/PKG signaling [95–97]. Stimulation of the PKG–dependent pathway has been demonstrated to exert potent protective effects in a broad range of cardiovascular disease models, including hypertension, PAH, heart failure, hemolytic anemia, and infarct-reperfusion injury [95–99]. But, the application of the drugs in a large cohort of patients with CVD demonstrate responses to the treatment. Some validated ways have been developed to enhance systemic and local NO levels and are promising in mediating the beneficial effects in CVD. But, to translate the research innovations into the application to a large population, more research is necessary, with particular attention to the effectiveness of the diet and strategies of increasing nNOS and improving NO–effector interactions in CVD settings. The NO and NOSs regulate myocardial contraction, relaxation, and pathological signaling are advanced, but the changing paradigm in the myocardium is not offered. NO from sources supplying the NO in the myocardium, and effectiveness of NO is confirmed by regulation mechanisms containing daily consumption of NO precursors, nitrate from skeletal muscles, NO production through the entire salivary NO pathway and from NOSs as well as the abundance of target proteins. In general, NO regulates downstream effector proteins through three mechanisms (sGcGMP/PKG-dependent phosphorylation, S–nitrosylation, and trans-nitrosylation) and the numbers and types of effectors regulated by NO are diverse. As such, modification of these effectors by NO subsequently triggers an array of signaling cascades that lead to different physiological and pathological consequences. By and large, NO and its downstream signaling pathway exert high cardiovascular protection; but, research of NO and NOS that are feasible for CVD and therapeutic efficiency using an NO–dependent regime are still far from satisfactory [11].

References

1. Arnold WP, Mittal CK, Katsuki S, Murad F (1977) Nitric oxide activates guanylate cyclase and increases guanosine 3’5’-cyclic monophosphate levels in various tissue preparations. Proc Natl Acad Sci 74: 3203–3207. Link: https://goocz.g6dRmID
2. Furchgott RF, Zawadzki JV (1980) the obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288: 373–376. Link: https://goocz.gTZWJ1
3. Gruetter CA, Barry BK, McNamara DB, Gruetter DY, Kadowitz PJ, et al. (1979) Relaxation of the bovine coronary artery and activation of coronary arterial guanylate cyclase by nitric oxide, nitroprusside and a carcinogenic nitrosamine. J Cyclic Nucleotide Res 5: 211–224. Link: https://goocz.gSNcD3
4. Massion PB, Feron O, Desy C, Balligand JL (2003) Nitric oxide and cardiac function: ten years after, and continuing. Circ Res 93: 388–396. Link: https://goocz.gPExcjT
5. Shah AM, MacCarthy PA (2000) Paracrine and autocrine effects of nitric oxide on myocardial function. Pharmacol Ther. 86: 49–86. Link: https://goocz.gFct4Tw
6. Xu KY, Huso DL, Dawson TM, Bredt DS, Becker LC (1999) Nitric oxide synthase in cardiac sarcoplasmic reticulum. Proc Natl Acad Sci 96: 657–662. Link: https://goocz.g4mX6Rl
7. Zhang YH, Jin CZ, Jing JH, Wang Y (2014) Molecular mechanisms of neuronal nitric oxide synthase in cardiac function and pathophysiology. J Physiol 592: 3169–3200. Link: https://goocz.gItRiD
8. Zhang YH, Casadei B (2012) Sub-cellular targeting of constitutive NOS in health and disease. J Mol Cell Cardiol 52: 341–350. Link: https://goocz.gSmU5g
9. Omar SA, Webb AJ (2014) Nitrite reduction and cardiovascular protection. J Mol Cell Cardiol 73: 57–65. Link: https://goocz.gVZcqjA
10. Castiglione N, Rinaldo S, Giardina G, Stelitano V, Cutruzzola F (2012) Nitric oxide and nitrate reductases: from molecular mechanisms to significance in human health and disease. Antioxid Redox Signal 17: 684–716. Link: https://goocz.gZ9MjFk
11. Lundberg JO, Gladwin MT, Weitzberg E (2015) Strategies to increase nitric oxide signaling in cardiovascular disease. Nat Rev Drug Discov 14: 623–641. Link: https://goocz.gUVmYK5
12. Doel JJ, Godber BL, GoulT TA, Eisenthal R, Harrison R (2000) Reduction of organic nitrates to nitric oxide catalyzed by xanthine oxidase: possible role in the metabolism of nitrovasodilator. Biochim Biophys Res Commun 270: 885–888. Link: https://goocz.g3FPUGk
13. Zhang Z, Naughton DP, Blake DR, Benjamin N, Stevens CR, et al. (1997) Human xanthine oxidase converts nitrite ions into nitric oxide (NO). Biochem Soc Trans 25: S245. Link: https://goocz.gNYt1K
14. Cosby K, Partovi KS, Crawford JH, Patel RP, Reiter CD, et al. (2003) Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. Nat Med 9: 1498–1505. Link: https://goocz.gXBiQWi
15. Rassaf T, Flögel U, Dreghone C, Hendgen-Cotta U, Kelm M, et al. (2007) Nitrite reductase function of deoxymyoglobin: oxygen sensor and regulator of cardiac energetics and function. Circ Res 100: 1749–1754. Link: https://goocz.gAM3Eri
16. Shiva S, Huang Z, Grubina R, Sun J, Ringwood LA, et al. (2007) Deoxymyoglobin is a nitrite reductase that generates nitric oxide and regulates mitochondrial respiration. Circ Res 100: 654–661. Link: https://goocz.gP4NcAg
17. Petersen MG, Dewilde S, Fago A (2008) Reactions of ferrous neuroglobin and cytoglobin with nitrate under anaerobic conditions. J Inorg Biochem 102: 1777–1782. Link: https://goocz.g3wjKr3
18. Kozlov AV, Staniek K, Nohl H (1999) Nitrite reductase activity is a novel function of mammalian mitochondria. FEBS Lett 454: 127–30. Link: https://goocz.gWNLeEQ
19. Kozlov AV, Dietrich B, Nohl H (2003) Various intracellular compartments cooperate in the release of nitric oxide from glycerol trinitrate in the liver. BR J Pharmacol 139: 989–997. Link: https://goocz.gNzSd47

Citation: Kivrak T, Erdem K, Karaca I (2017) Nitric oxide functions in the heart. Arch Anat Physiol 2(1): 020-026.
20. Li H, Cui H, Kundu TK, Alzawahra W, Zweier JL (2008) Nitric oxide production from nitrite occurs primarily in tissues not in the blood: critical role of xanthine oxidase and aldehyde hydrolase. J Biol Chem 283: 17855–17863. Link: https://doi.org/MyQ37

21. Aamand R, Dalsgaard T, Jensen FB, Simonsen U, Roepstorff A, et al. (2009) Generation of nitric oxide from nitrite by carbonic anhydrase: a possible link between metabolic activity and vasodilatation. Am J Physiol Heart Circ Physiol 297: H2068–H2074. Link: https://doi.org/ng8MgH

22. Vanin AF, Bevers LM, Slama-Schwok A, van Faassen EE (2007) Nitric oxide synthase reduces nitrite to NO under anoxia. Cell Mol Life Sci 64: 96–103. Link: https://doi.org/yt4QSF

23. Pennington JA (1998) Dietary exposure models for nitrates and nitrites. Food Control 9: 385–395. Link: https://doi.org/G7Zwd8

24. Piknova B, Park JW, Swanson KM, Dey S, Nugochi CT, et al. (2015) Skeletal muscle as an endogenous nitrate reservoir. Nitric Oxide 47: 10–16. Link: https://doi.org/D2NzTz

25. Percival JM, Anderson KN, Huang P, Adams ME, Froehner SC (2010) Golgi and sarcocellular neuronal NOS differentially regulate contraction-induced fatigue and vasoconstriction in exercising mouse skeletal muscle. J Clin Invest 120: 816–826. Link: https://doi.org/RWCSiS

26. Balland JL, Feron O, Dessy C (2009) eNOS activation by physical forces: from short-term regulation of contraction to chronic remodeling of cardiovascular tissues. Physiol Rev 89: 481–534. Link: https://doi.org/YQRSs5

27. Villanueva C, Giulivi C (2010) Subcellular and cellular locations of nitric oxide synthase isoforms as determinants of health and disease. Free Radic Biol Med 49: 307–316. Link: https://doi.org/TvV3L

28. Goligorsky MS, Li H, Brodsky S, Chen J (2002) Relationships between caveolae and sarcocellular neuronal NOS differentially regulate contraction-induced fatigue and nitric oxide synthase to endothelial cell caveolae via palmitoylation: implications for nitric oxide signaling. Proc Natl Acad Sci 93: 6448–6453. Link: https://doi.org/B2sokk

29. Piech A, Massert PE, Dessy C, Feron O, Havaux X, et al. (2002) Decreased expression of myocardial eNOS and caveolin in dogs with hypertrophic cardiomyopathy. Am J Physiol Heart Circ Physiol 283: F1–10. Link: https://doi.org/3wCZQ

30. García-Cardeña G, Oh P, Liu J, Schnitzer JE, Sessa WC (1996) Targeting of myocardial nitric oxide synthase and caveolin in dogs with hypertrophic cardiomyopathy. J Biol Chem 271: 11820–11828. Link: https://doi.org/6wuxgE

31. Bendall JK, Damy T, Ratajczak P, Loyer X, Monceau V, et al. (2004) Role of myocardial neuronal nitric oxide synthase-derived nitric oxide in beta-adrenergic hyporesponsiveness after myocardial infarction-induced heart failure. Sci Signal 7: ra27. Link: https://doi.org/FXdN

32. Jin CZ, Jang JH, Ko GP, Kim SJ, Yi EC, et al. (2013) Myofilament Ca2+ desensitization mediates the positive lusitropic effect of neuronal nitric oxide synthase in left ventricular myocytes from the murine hypertensive heart. J Mol Cell Cardiol 60: 107–115. Link: https://doi.org/hkHntpM

33. Aquilano K, Baldelli S, Cirilo MR (2014) Nuclear recruitment of neuronal nitric oxide synthase by α-synuclein is crucial for the induction of mitochondrial biogenesis. J Biol Chem 289: 365–378. Link: https://doi.org/sbK2h5

34. Jiang JH, Kang MJ, Ko GP, Kim SJ, Yi EC, et al. (2015) Identification of a novel splice variant of neuronal nitric oxide synthase, nNOS3, in myofilament fraction of murine cardiomyocytes. Nitric Oxide 50: 20–27. Link: https://doi.org/96qQn

35. Barouch LA, Harrisson RW, Skaf MW, Rosas GO, Cappola TP, et al. (2002) Nitric oxide regulates the heart by spatial confinement of nitric oxide synthase isoforms. Nature 416: 337–339. Link: https://doi.org/jT6BW

36. Damy T, Ratajczak P, Shah AM, Camors E, Marty I, et al. (2004) Increased neuronal nitric oxide synthase-derived NO production in the failing human heart. Lancet 363: 1365–1367. Link: https://doi.org/zxar91

37. Sun J, Picht E, Ginsburg KS, Bers DM, Steenbergen C, et al. (2006) Hypercontractile female hearts exhibit increased S-nitrosylation of the L-type Ca2+ channel alpha one subunit and reduced ischemia/reperfusion injury. Circ Res 98: 403–11. Link: https://doi.org/FKrWqQ

38. Petroff MG, Kim SH, Pepe S, Dassy C, Marbán E, et al. (2001) Enzyme-catalyzed reactions mediate the stretch dependence of Ca2+ release in cardiomyocytes. Nat Cell Biol 3: 867–873. Link: https://doi.org/kTuEa

39. Jin Z, Han H, Zhang T, Puglisi J, Izu L T, et al. (2014) Mechanocancherotransduction during cardiomyocyte contraction is mediated by localized nitric oxide signaling. Sci Signal 7: ra27. Link: https://doi.org/bmtqNq

40. Wynia-Smith SL, Smith BC (2017) Nitrosothiol formation and S-nitrosation signaling through nitric oxide synthases. Nitric Oxide 63: 52–60. Link: https://doi.org/Upk4w

41. Murphy E, Kohr M, Menazza S, Nguyen T, Evangelista A, et al. (2014) Signaling by S-nitrosylation in the heart. J Mol Cell Cardiol 73: 18–25. Link: https://doi.org/6wuxgE

42. Kohr MJ, Murphy E, Steenbergen C (2014) Glyceroldehyde-3-phosphate Dehydrogenase acts as a mitochondrial trans-S-nitrosyl rat in the heart. PLoS One 9: e111448. Link: https://doi.org/kM8KfF

43. Burgoyne JR, Eaton P (2009) Transnitrosylating nitric oxide species directly activate type I protein kinase A, providing a new adenylyl cyclase-dependent Cross-Talk to beta-adrenergic-like signaling. J Biol Chem 284: 29260–29268. Link: https://doi.org/RiKUsT

44. Benhar M, Forrester MT, Stamler JS (2009) Protein denitrosylation: enzymatic mechanisms and cellular functions. Nat Rev Mol Cell Biol 10: 721–732. Link: https://doi.org/WmNPp

45. Foster MW, Hess DT, Stamler JS (2009) Protein S-nitrosylation in health and disease: A current perspective. Trends Mol Med 15: 391–404. Link: https://doi.org/KhZRC

46. Zhang YH, Zhang MH, Sears CE, Emanuel K, Redwood C, et al. (2008) Reduced phospholamban phosphorylation is associated with impaired relaxation in left ventricular myocytes from neuronal NO synthase-deficient mice. Circ Res 102: 242–249. Link: https://doi.org/5WnHx

47. Hammond J, Balland JL (2012) Nitric oxide synthase and cyclic GMP signaling in cardiac myocytes: from contractility to remodeling. J Mol Cell Cardiol 52: 330–340. Link: https://doi.org/Wei9Pc

48. Idigo WO, Reilly S, Zhang MH, Zhang YH, Jayaram R, et al. (2012) Regulation of endothelial nitric-oxide Synthase (NOS) S-glutathionylation by neuronal NOS: evidence of a functional interaction between myocardial constitutive NOS isoforms. J Biol Chem 287: 43665–43673. Link: https://doi.org/76oxNV

49. Jin CZ, Jang JH, Wang Y, Jang JH, Wang Y, et al. (2012) Neuronal nitric oxide synthase is up-regulated by angiotensin II and attenuates NADPH oxidase activity and facilitates relaxation in murine left ventricular myocytes. J Mol Cell Cardiol 52: 1274–1281. Link: https://doi.org/4QlFU

50. Zhang YH, Dingle L, Hall R, Casadei B (2009) The role of nitric oxide and reactive oxygen species in the positive inotropic response to mechanical stretch in the mammalian myocardium. Biochim Biophys Acta 1787: 811–817. Link: https://doi.org/EqgBn

51. Burkard N, Williams T, Czolbe M, Blömer N, Panther F, et al. (2010) Conditional overexpression of neuronal nitric oxide synthase is cardioprotective in ischemia/reperfusion. Circulation 122: 1588–1603. Link: https://doi.org/w4Rgqx

52. Adachi T, Weisbord RM, Pimentel DR, Ying J, Sharov VS, et al. (2004) S-Glutathionylation by peroxynitrite activates SERCA during arterial relaxation by nitric oxide. Nat Med 10: 1200–1207. Link: https://doi.org/npMqGG

53. Pastore A, Piemonte F (2013) Protein glutathionylation in cardiovascular diseases. Int J Mol Sci 14: 20845–20876. Link: https://doi.org/R9briz
54. Capettini LS, Cortes SF, Gomes MA, Silva GA, Pesquero JL, et al. (2008) Neuronal nitric oxide synthase-derived hydrogen peroxide is a major endothelium-dependent relaxing factor. Am J Physiol Heart Circ Physiol 295: H2503–H2511. Link: https://goo.gl/3d3a8x

55. Capettini LS, Cortes SF, Lemos VS (2010) Relative contribution of eNOS and nNOS to endothelium-dependent vasodilation in the mouse aorta. Eur J Pharmacol 643: 260–266. Link: https://goo.gl/joEIty

56. Rabelo LA, Cortes SF, Alvarez-Leite JL, Lemos VS (2003) Endothelium dysfunction in LDL receptor knockout mice: a role for H2O2. Br J Pharmacol 138: 1215–1220. Link: https://goo.gl/gbMjZF

57. Capettini LS, Cortes SF, Silva JF, Alvarez-Leite JL, Lemos VS (2011) Decreased production of neuronal NOS-derived hydrogen peroxide contributes to endothelial dysfunction in atherosclerosis. Br J Pharmacol 164: 1738–1748. Link: https://goo.gl/scGZ2f

58. Silva GC, Silva JF, Diniz TF, Lemos VS, Cortes SF (2016) endothelial dysfunction in DOCA-salt-hypertensive mice: the role of neuronal nitric oxide synthase-derived hydrogen peroxide. Clin Sci (Lond) 130: 895–906. Link: https://goo.gl/k8h91Y

59. Brennan JP, Bardswell SC, Burgoyne JR, Fuller W, Schröder E, et al. (2006) Oxidant-induced activation of type I protein kinase A is mediated by Ri subunit interprotein disulfide bond formation. J Biol Chem 281: 21827–21836. Link: https://goo.gl/udjN17

60. Burgoyne JR, Madhani M, Cuello F, Charles RL, Brennan JP, et al. (2007) Cysteine redox sensor in PKGⅳa enables oxidant-induced activation. Science 317: 1393–1397. Link: https://goo.gl/kscGEc

61. Kohr MJ, Davis JP, Ziolo MT (2009) Peroxynitrite Increases Protein Phosphatase Activity and Promotes the Interaction of Phospholamban with Protein Phosphatase 2a in the Myocardium. Circ Res 105: 383–392. Link: https://goo.gl/0e8Hqf

62. Crabtree MJ, Tatham AL, Al-Wakeel Y, Warrick N, Hale AB, et al. (2009) Association of plasma asymmetrical dimethylarginine (ADMA) with elevated vascular superoxide production and endothelial nitric oxide synthase (NOS) activity. Free Radic Biol Med 47: 264–266. Link: https://goo.gl/jV5Xyz

63. Chen CA, Wang TY, Varadharaj S, Reyes LA, Hemann C, et al. (2010) Cysteine redox sensor in PKGⅳa enables oxidant-induced activation. Science 317: 1393–1397. Link: https://goo.gl/kscGEc

64. Antoniades C, Shirodaria C, Leeson P, Antonopoulos A, Warrick N, et al. (2008) Cardiac capsaicin-sensitive sensory nerves regulate myocardial relaxation via S-nitrosylation of SERCA. Br J Pharmacol 153: 488–496. Link: https://goo.gl/PjGxNf

65. Sears CE, Bryant SM, Ashley EA, Lygate CA, Rakovic S, et al. (2013) Cardiac neuronal nitric oxide synthase-derived hydrogen peroxide contributes to endothelial dysfunction in atherosclerosis. Br J Pharmacol 164: 1738–1748. Link: https://goo.gl/scGZ2f

66. Crabtree MJ, Tatham AL, Al-Wakeel Y, Warrick N, Hale AB, et al. (2009) Association of plasma asymmetrical dimethylarginine (ADMA) with elevated vascular superoxide production and endothelial nitric oxide synthase (NOS) activity. Free Radic Biol Med 47: 264–266. Link: https://goo.gl/jV5Xyz

67. Dedková EN, Blatter LA (2006) Mitochondrial calcium uptake stimulates nitric oxide and ROS production by mitochondria-specific nitric oxide synthase (mtNOS) in cat ventricular myocytes. Biophys J 90: 521. Link: https://goo.gl/saXu5j

68. Figueiredo-Freitas C, Dulce RA, Foster MW, Liang J, Yamashita AM, et al. (2015) S-Nitrosylation of Sarcomeric Proteins Depresses Myofilament Ca2+ Sensitivity in Intact Cardiomyocytes. Antioxid Redox Signal 23: 1017–1034. Link: https://goo.gl/ix9L7X

69. Burger DE, Lu X, Lei M, Xiang FL, Hammoud L, et al. (2009) Neuronal nitric oxide synthase protects against myocardial infarction-induced ventricular arrhythmia and mortality in mice. Circulation 120: 1345–1354. Link: https://goo.gl/g3FMsf

70. Cutler MJ, Plummer BN, Wan X, Sun QA, Hess D, et al. (2012) Aberrant S-nitrosylation mediates calcium-triggered ventricular arrhythmia in the intact heart. Proc Natl Acad Sci 109: 1818–1819. Link: https://goo.gl/8jPtG0

71. Núñez L, Vaquero M, Gómez R, Caballero R, Mateos-Cáceres P, et al. (2006) Nitric oxide blocks hKv1.5 channels by S-nitrosylation and by a cyclic GMP-dependent mechanism. Cardiovasc Res 72: 80–89. Link: https://goo.gl/v5Xyz

72. Gómez R, Caballero R, Barana A, Amorós I, Calvo E, et al. (2009) Nitric oxide increases cardiac IK1 by nitrosylation of cysteine 76 of Kir2.1 channels. Circ Res 105: 383–392. Link: https://goo.gl/0e8Hqf

73. Asada K, Kurokawa J, Furukawa T (2009) Redox- and calmodulin-dependent S-nitrosylation of the KCNQ1 channel. J Biol Chem 284: 6014–6020. Link: https://goo.gl/jB6x2b

74. Bencok P, Kupai K, Gíriz Z, Góbre, A, HúlikÁ, et al. (2008) Cardiac capsaicin-sensitive sensory nerves regulate myocardial relaxation via S-nitrosylation of SERCA. Br J Pharmacol 153: 488–496. Link: https://goo.gl/PjGxNf

75. Layland J, Jia-Mei Li, Ajay M Shah (2002) Role of cyclic GMP-dependent protein kinase in the contractile response to exogenous nitric oxide in rat cardiac myocytes. J Physiol 540: 457–467. Link: https://goo.gl/5buSuj

76. Figueiredo-Freitas C, Dulce RA, Foster MW, Liang J, Yamashita AM, et al. (2015) S-Nitrosylation of Sarcomeric Proteins Depresses Myofilament Ca2+ Sensitivity in Intact Cardiomyocytes. Antioxid Redox Signal 23: 1017–1034. Link: https://goo.gl/ix9L7X

77. Dedková EN, Blatter LA (2006) Mitochondrial calcium uptake stimulates nitric oxide and ROS production by mitochondria-specific nitric oxide synthase (mtNOS) in cat ventricular myocytes. Biophys J 90: 521. Link: https://goo.gl/saXu5j

78. Erusalimsky JD, Moncada S (2007) Nitric oxide and mitochondrial signaling: from physiology to pathophysiology. Arterioscler Thromb Vasc Biol 27: 2524–2531. Link: https://goo.gl/xQeCcs

79. Chouchani ET, Methner C, Nadtochiy SM, Logan A, Pell VR, et al. (2013) Cardioprotection by S-nitrosation of a cysteine switch on mitochondrial complex I. Nat Med 19: 753–759. Link: https://goo.gl/u1L1z2

80. Welter R, Yu L, Yu CA (1996) The effects of nitric oxide on electron transport complexes. Arch Biochem Biophys 331: 9–14. Link: https://goo.gl/GmrxqX

81. Torres J, Darley-Usmar V, Wilson MT (1995) Inhibition of cytochrome c oxidation by neurotransmitters: implications for control of respiration. Biochem J 312: 169–173. Link: https://goo.gl/66j1SD

82. Grozdanovic Z (2001) NO message from muscle. Microsc Res Tech 55: 148–153. Link: https://goo.gl/WuoQYX

83. Sarti P, Arese M, Forte R, Giummarie A, Maestroni G, et al. (2012) Mitochondrial and nitric oxide: chemistry and pathophysiology. Adv Exp Med Biol 942: 75–92. Link: https://goo.gl/1xQQ2Q

84. Wadley GD, Choi OE, McConnell K (2007) NOS isoform-specific regulation of basal but not exercise-induced mitochondrial biogenesis in mouse skeletal muscle. J Physiol 585: 253–262. Link: https://goo.gl/VfYBej

85. Gutsaeva DR, Carraway MS, Suliman HB, Demchenko IT, Shitara H, et al. (2008) Transient hypoxia stimulates mitochondrial biogenesis in brain subcortex by a neuronal nitric oxide synthase-dependent mechanism. J Neurosci 28: 2015–2024. Link: https://goo.gl/upS0q

Citation: Kivrik T, Erdem K, Karaca I (2017) Nitric oxide functions in the heart. Arch Anat Physiol 21(1): 020-026.
86. Baldelli S, Lettieri Barbato D, Tatulli G, Aquilano K, Cirillo MR (2014) The role of nNOS and PGC-1α in skeletal muscle cells. J Cell Sci 127: 4813–4820. Link: https://goo.gl/v5cuoSB

87. Sobko T, Marcus C, Govoni M, Kaniya S (2010) Dietary nitrate in traditional Japanese foods lowers diastolic blood pressure in healthy volunteers. Nitric Oxide 22: 136–140. Link: https://goo.gl/IAAJM

88. Rathod KS, Velmurugan S, Ahluwalia A (2016) A ‘green’ diet-based approach to cardiovascular health? Is inorganic nitrate the answer?. Mol Nutr Food Res 60: 185–202. Link: https://goo.gl/1Ra45x

89. Hord NG, Tang Y, Bryan NS (2009) Food sources of nitrates and nitrates: the physiologic context for potential health benefits. Am J Clin Nutr 90: 1–10. Link: https://goo.gl/7Ul6FLi

90. Charles RL, Rudyk O, Prysyazhna O, Kamynina A, Yang J, et al. (2014) Protection from hypertension in mice by the Mediterranean diet is mediated by nitro fatty acid inhibition of soluble epoxide hydrolase. Proc Natl Acad Sc 111: 8167–8172. Link: https://goo.gl/C8xFkc

91. Kureishi Y, Luo Z, Shiojima I, Bialik A, Fulton D, et al. (2000) The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. Nat Med 6: 1004–1010. Link: https://goo.gl/eFxjb

92. Kosmidou I, Moore JP, Weber M, Searles CD (2007) Statin treatment and 3’ polyadenylation of eNOS mRNA. Arterioscler Thromb Vasc Biol 27: 2642–2649. Link: https://goo.gl/ahm9Hw

93. Salloum F, Yin C, Xi L, Kukreja RC (2003) Sildenafil induces delayed preconditioning through inducible nitric oxide synthase-dependent pathway in mouse heart. Circ Res 92: 595–597. Link: https://goo.gl/XtxwHj

94. Michelakis E, Tymchak W, Lien D, Webster L, Hashimoto K, et al. (2002) Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. Circulation 105: 2398–2403. Link: https://goo.gl/fmmnJR

95. Stasch JP, Pacher P, Evgenov OV (2011) Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. Circulation 123: 2263–2273. Link: https://goo.gl/n3qbM

96. Raat NJ, Tabima DM, Specht PAC, Tejero J, Champion HC, et al. (2013) Direct sGC activation bypass NO scavenging reactions of intravascular free oxyhemoglobin and limits vasconstriction. Antioxid Redox Signal 19: 2232–2243. Link: https://goo.gl/nFHnZx

97. Thadani U, Smith W, Nash S, Bittar N, Glasser S, et al. (2002) the effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. J Am Coll Cardiol 40: 2006–2012. Link: https://goo.gl/AM7m1w

98. Michelakis E, Tymchak W, Lien D, Webster L, Hashimoto K, et al. (2002) Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. Circulation 105: 2398–2403. Link: https://goo.gl/fmmnJR