Curr Emerg Hosp Med Rep (2017) 5:41–46
DOI 10.1007/s40138-017-0132-7

The Use of Nitrates in the Management of Acute Heart Failure in the Emergency Department: a Review

Andrew Bolano[1] · **Mohammed Alzahri**[2,3]

Published online: 3 April 2017

Abstract
Purpose of Review Nitrates represent a frequently used group of medications in the management of hypertensive patients in acute heart failure. Despite its longevity, usage of this medication seems to be guided chiefly by expert opinion, with relatively few trials involving interventions in the emergency department. This review seeks to define more precisely the role of nitrates in the emergency department by discussing some of the more compelling research that exists on the topic in addition to their biochemistry and current guidelines.
Recent Findings More recent explorations have demonstrated various benefits to regimens of high dose nitrates started in the emergency department such as lower rates of ICU admission and endotracheal intubation. The more feared complications of nitrate use, namely hypotension, do not see an increase in incidence with increase in dosages.
Summary High-quality trials that demonstrate either optimal dosage of nitrates and even explicit hemodynamic or mortality benefits associated with their use still eludes us. Current recommendations and expert opinion continue to guide therapy while evidence that does exist suggests possible equivalency of high dose intermittent administration to titratable infusion. As nitrates have long been a cornerstone in the management of pulmonary congestion in acute heart failure, a true double-blinded RCT to demonstrate their benefits may not be practical. In light of this, current evidence suggests that future research on dosage and route of administration may help to minimize cost associated with hospitalization (e.g., ETT, ICU admissions, drips).

Keywords Nitrates · Nitroglycerine · Acute heart failure · Congestive heart failure · Pulmonary congestion · Pulmonary edema · Vasodilatation

This article is part of the Topical Collection on *Heart Failure*

✉ Andrew Bolano
bolano@bcm.edu

Mohammed Alzahri
Mohammad.Alzahri@bcm.edu

[1] Department of Emergency Medicine, Baylor College of Medicine, 1 Baylor Plaza, Room BCMM-M220, Houston, TX 77030, USA

[2] King Saud University, King Khalid Rd, Riyadh 12372, Saudi Arabia

[3] Baylor College of Medicine, Department of Emergency Medicine, 1504 Ben Taub Loop, Room BTGH-1EC, Houston, TX 77030, USA

Introduction

Heart failure represents a common pathophysiologic endpoint for many heterogeneous cardiovascular diseases. While the classifications of heart failure are legion (i.e., acute vs. chronic, compensated vs. decompensated, and systolic vs. diastolic), all states represent a reduction of the heart's capacity to maintain cardiac output in the setting of otherwise adequate filling pressures. Common signs of heart failure include edema, fluid retention, orthopnea, and dyspnea on exertion. Among these, acute heart failure (AHF) is the rapid onset or rapid worsening of these symptoms and frequently requires hospitalization. It is an increasingly common chief complaint in emergency centers, averaging close to one million emergency department (ED) visits annually from 2006 to 2010, with admission rates that exceeded 80% [1].

Given the financial implications, it is interesting that management principles of AHF have not changed significantly over the last 40 years [2•] and that in-hospital and 1-year outcomes of this patient group remain high. This is in contrast

to outpatient management of chronic heart failure (CHF), which demonstrates an overall positive trend in outcomes [3].

In addition to I.V. diuretics, nitrates have long been a cornerstone in management of the hypertensive subset of AHF patients, a subset which represents the vast majority of AHF patients. The "organic nitrates" include nitroglycerin (glyceryl trinitrate—GTN), isosorbide mononitrate (ISMN), isosorbide dinitrate (ISDN), and pentaerythritol tetranitrate (PETN) and have been frequently used in hospitalized patients with AHF for decades. Despite this long-standing presence, explicit evidence defining their actual benefits to patients and optimal dosing strategies is sparse. This paper will review the most current recommendations and the existing evidence for nitrate use in AHF in the emergency department, with a discussion of the biochemistry and directions for future research in defining their role in clinical practice.

Recommendations and Current Practice Patterns

With respect to hospitalized patients with heart failure, ACC/AHA guidelines currently suggest that in the absence of hypotension I.V. nitroglycerin, nitroprusside or nesiritide can be an adjunct therapy to diuretic therapy for symptomatic improvement in patients with AHF [4]. This evidence is given an "A" level and ranked as class IIB based on three studies. Notably for emergency providers, none of the arms of the studies in these papers involved an emergency department population, instead focusing only on hospitalized patients.

Similarly, the ESC guidelines from 2016 suggest aggressive blood pressure reduction by approximately 25% within the first few hours with IV vasodilators in combination with diuretics [5]. However, in a follow-up subsection, the authors comment that while I.V. vasodilators are the second most common agents in hypertensive AHF for symptomatic relief, they did not find "robust" evidence of their benefits and no dosing recommendations are provided. Again, recommendations here are based on three studies (one overlapping with ACC guidelines), only one of which features emergency department intervention and nitrates.

Notably, neither organization offers dosing suggestions to guide practitioners in their treatment. In the literature, GTN infusion dosing differs between studies without clear superiority and is often left up to the discretion of the treating physician, ranging from 13 μg/min to high doses of 2 mg every 2 min (mean of 6.5 mg) [6••, 7]. Textbook standards suggest starting NTG I.V. at 0.5–0.7 μg/kg/min up to 200 μg/min, blood pressure permitting, while other peer-reviewed resources offer a higher 5–10 μg/min starting point with small titrations every few minutes up to 200 μg/min. For hypertension recalcitrant to NTG, nitroprusside may be initiated at similar starting doses (0.3–0.5 μg/kg/min) to a maximum of 10 μg/kg/min (or 400 μg/min) [8, 9].

There is a significant disconnect between these "common sense" or "expert opinion" based recommendations and current practice patterns, as suggested by Maggioni et al. in an analysis of multiple patient registries [3]. They found that the recommendations of the 2012 ESC guidelines, which placed AHF patients into three strata based on blood pressure, were not typically adhered to. Inotrope administration was found in inappropriately high blood pressure groups and nitrates were used less frequently than recommended in the hypertensive groups. This disconnect may be a manifestation of the fact that the patient hospitalized with AHF has been shown to be significantly different than those enrolled in the randomized controlled trials (RCT) that were performed [2•, 10]. Compared to the 2012 guidelines, the most recent ACC and ESC guidelines on heart failure are based more on clinical assessment rather than specific parameters, perhaps in recognition of this phenomenon and the nature of evidence that does exist for acute heart failure management (Fig. 1) [5, 11].

Biochemistry/Mechanism

Historically, agents such as nitroglycerin, ISDN, ISMN, PETN, and nitroprusside have been grouped together as "nitrates" and described homogenously as nitric oxide (NO) group donors. While nitroprusside actually spontaneously releases NO, the other nitrates undergo an enzymatic process during bioactivation. In a dose-dependent manner, these agents first cause dilation of the veins followed by the arteries (including coronaries), which reduces systemic vascular resistance, pulmonary vascular resistance, and left ventricular filling pressure (left ventricular end-diastolic volume).

NO is an activator of smooth muscle soluble guanylate cyclase, which forms cyclic GMP, inhibits intracellular calcium flow, and thereby mediates smooth muscle relaxation. These agents (as well as all other vasodilators) are also subject to a phenomenon called pseudotolerance or tachyphylaxis, whereby their hemodynamic effects cause activation of neurohormonal cascade (i.e., RAAS axis), which directly oppose these effects by increasing sodium, water retention, stimulating catecholamine release [2•, 8, 12].

While previously regarded as a common group, current understanding of the enzymatic pathways demonstrates that these agents have heterogenous features that may direct future clinical applications. This is especially the case for the oldest and most well-known nitrate, nitroglycerin (GTN), where bioactivation via cytosolic and mitochondrial aldehyde dehydrogenase 2 (ALDH2) with subsequent inactivation of ALDH2 by superoxide species has been shown to be the likely mechanism of activity and "true" tolerance [13, 14••, 15]. While NTG participates in mitochondrial metabolism, other nitrates interact with the P450 system (Fig. 2). The superoxide species generated by GTN metabolism also compound the

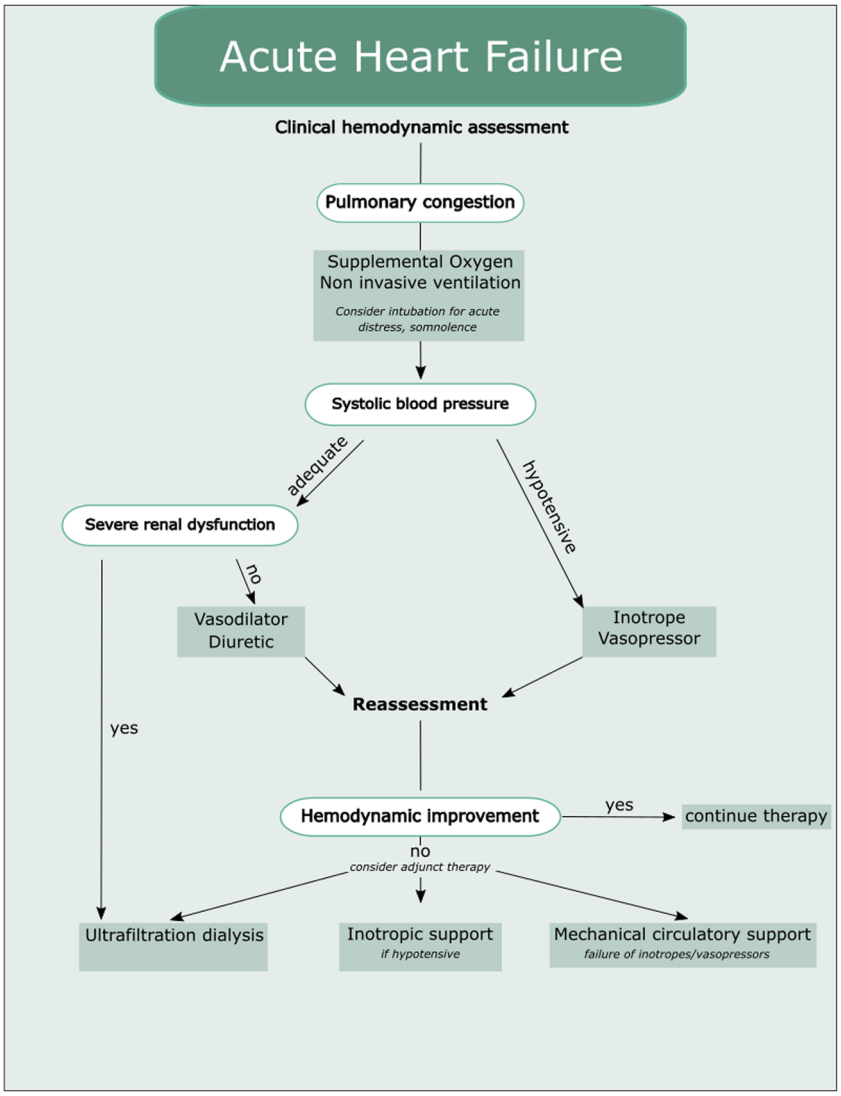

Fig. 1 Algorithm for management of heart failure with pulmonary congestion, derived from ESC guidelines 2011, 2016, and ACC guidelines 2013 [4, 5, 11]. Based on a clinical assessment of respiratory status and blood pressure, treatment should be considered as indicated in the flow chart with possible adjunct therapies for failure to respond to titration of initial management. Hypotension is defined as SBP <90 mmHg. Mechanical circulatory support includes aortic balloon pump, extracorporeal membrane oxygenation, and left ventricular assist device

tachyphylaxis phenomenon by creating supersensitivity to vasoconstrictors. When looking at other nitrates for signs of endothelial stress and vascular tolerance, it is demonstrable that ISMN and PETN have no true vascular tolerance and PETN actually upregulates protective antioxidant proteins [14••], although specific pathways have not been elucidated for these agents.

Current Evidence

Based on this "classic" mechanism, nitrates as a group should be ideal agents for optimizing the Frank-Starling curve in a patient experiencing hypertensive AHF complicated by pulmonary edema. While some studies exist that show improvements in in-hospital outcomes, hemodynamic parameters, and microcirculatory effects, there is no well-powered RCT that demonstrates improved morbidity/mortality of nitrate use in patients presenting to the ED in AHF.

A widely cited study, performed by Cotter et al., compared high-dose Lasix + low-dose ISDN with low-dose Lasix + high-dose ISDN [16]. The authors found in the latter group of 110 patients that the rates of myocardial infarction (MI) and mechanical intubation due to severe pulmonary edema were lower. In another trial, the same group demonstrated improved O_2 saturation and mean arterial pressure (MAP) reduction when high-dose ISDN was used. The study also indicated that there were decreased rates of death, MI, and intubation in the high-dose ISDN (4 mg bolus every 4 min) arm over the low-dose ISDN (10 μmol/min titrated up by 10 μmol every 10 min) + BiPAP arm to the degree that the study had to be concluded prematurely [17].

In a feasibility and outcome analysis, Levy et al. enrolled a small cohort (n = 23) of patients with pulmonary edema refractory to standard therapy to high-dose NTG (titratable

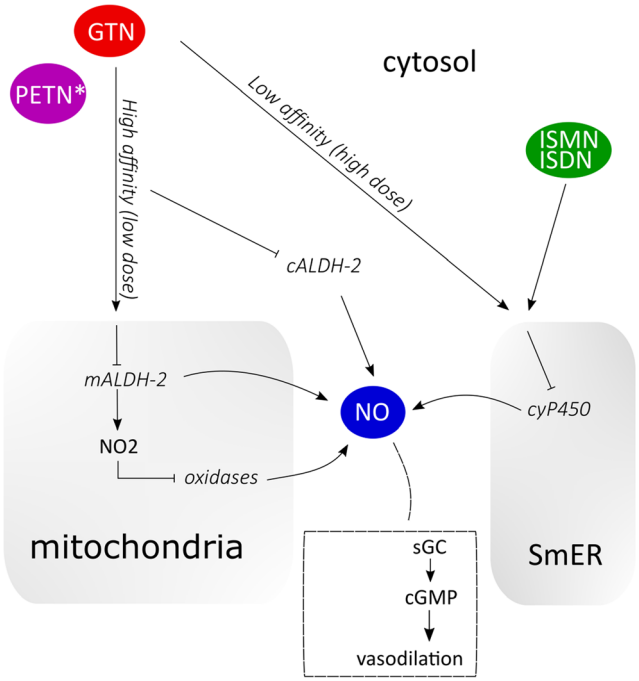

Fig. 2 Bioactivation of organic nitrates. GTN is metabolized by two chief pathways. High-dose/low-affinity pathway produces nitric oxide (NO) directly by interaction of both cytosolic and mitochondrial ALDH2. NO_2 that is produced may be reduced to NO by oxidases in the mitochondria or cytosol (not illustrated here). ISDN and ISMN or GTN at higher dosages are activated in the smooth endoplasmic reticulum by cytochrome P450 enzymes to form NO. SNP directly releases NO and CN radicals when interacting with oHgb, producing mHgb. NO subsequently activates its intracellular cascade: soluble guanylate cyclase upregulates cGMP, which activates cGMP-dependent kinases and ion channels, modulating calcium influx, resulting in relaxation of endothelial smooth muscle cells and vasodilation. PETN undergoes similar activation along the similar high-affinity pathway but has been shown not to induce free radical generation. *SmER* smooth endoplasmic reticulum, *GTN* glyceryl trinitrate (=nitroglycerin), *mALDH2/cALDH2* mitochondrial/cytosolic aldehyde dehydrogenase, *NO_2* nitrite, *NO* nitric oxide, *sGC* soluble guanylyl cyclase, *cGMP* cyclic guanosine monophosphate, *ISDN* isosorbide dinitrate, *ISMN* isosorbide mononitrate, *SNP* sodium nitroprusside, *oHgb* oxyhemoglobin, *mHgb* methemoglobin, *CN* cyanide. Adapted from Uil et al. [15]

infusion with 2 mg boluses at MD discretion every 3–5 min) and found decreased rates of intubation and no change in adverse cardiac events or symptomatic hypotension [18]. A follow-up study with a more sizable cohort (n = 366), albeit a single center study, compares this same intervention against a standard infusion and a combination of bolus and infusion respectively. The authors found a decreased ICU admission rate as before and no difference in adverse outcomes, although decreased intubation rates were not observed [19].

While these studies yielded encouraging results that seem to favor nitrate use and in high doses, there are significant limitations. The limitation of the first study (and reason why it was not included in a Cochrane review) is of course that nitrates are used in both arms of the intervention. Additionally, in the second study, nitrates were added on top of "standard of care" therapy that the investigators defined as furosemide, morphine, and O_2. Similarly, the feasibility analysis that prompted the third study performed an intervention on patients who had "failed standard management," which included the use of sublingual nitrates and furosemide. In the follow-up study, while the authors did randomize treatment from presentation, they concede that their hospital policy which mandates ICU admission for vasoactive infusion rates is a serious confounder. Ultimately, they present the bolus administration as a safe and cost-saving alternative given its equivalent outcomes.

While they may be methodologically sound, albeit small studies, they are predicated on the use of nitrates as a standard of care, even though this has yet to be established by a well-powered, placebo-controlled, double-blind RCT. In fact, the Vasodilatation in the Management of Acute CHF (VMAC) study compared the use of recombinant B-natriuretic peptide (nesiritide) against NTG and placebo arms, respectively. "Commonly used" doses of NTG had no benefit over placebo with regard to their primary outcomes of subjective dyspnea and clinical status and demonstrated no persistent hemodynamic differences beyond the first assessment point of 3 h [6••]. The NTG group was indeed found to be inferior to nesiritide at each time point as well. This may indicate inferiority or that the nitrate group (n = 143) was subjected to insufficient doses (median = 13 μg/min), as measurable effects on filling pressures and arterial pressures can be seen at infusion rates of 33 μg/min and higher [20], while significant arterial dilation can be achieved at doses of >250 μg/min [21].

A Cochrane review attempted to pool data on nitrate use in AHF, yet the authors were only able to find four studies that fit the criteria for inclusion, and even these yielded a fairly heterogeneous group [10]. Ultimately, they found that, with regard to primary outcome (e.g., symptomatic relief) and nearly all secondary outcomes (e.g., hemodynamic parameters, progression to intubation), there was insufficient evidence to make clinical recommendations for intravenous nitrate therapy over placebo.

Future Directions

In addition to endpoints such as MAP, O_2, endotracheal intubation, and others, some investigators have looked at biomarkers like brain natriuretic peptide (BNP) as a surrogate for cardiac stress and its response to early high-dose nitrates. Breidthardt et al. initiated high-dose sublingual nitrates combined with transdermal nitrates in the ED, resulting in significantly decreased BNP levels over 48 h and fewer ICU admissions, although 90-day mortality and hospital outcomes remained unaffected [22].

Based on the concept that AHF syndromes are characterized not only by gross hemodynamic changes but also dysfunction at the endothelial level [23], Uil et al. monitored the microcirculatory effects (e.g., perfused capillary density, PCD) of nitrate administration (33 μg/min) in 20 inpatients with AHF as well as pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP). They were able to demonstrate improved PCD and reduced PCWP and CVP at these low dosages in 70% of patients [20]. In a subgroup analysis, the authors propose that the other 30%, labeled "non-responders," were in clinically worse states of heart failure and thus would require higher doses of NTG to overcome their relatively worse endothelial dysfunction limited metabolism of NTG.

In consideration of the rapid tolerance seen with organic nitrates (NO^{-3}) and resistance that CHF patients demonstrate, nitrite (NO^{-2}) has been explored as an alternative. In a safety and feasibility study among a group of severe CHF patients on a cardiac transplant list, high-dose infusions of Na_2NO_2 (50 μg/kg/min) over a short period consistently increased CO and decreased pulmonary vascular resistance, right atrial filling pressure, systemic vascular resistance, with mild effect on MAPs, and no added morbidity or mortality [24]. Clearly, these patients are not the prototypical acute heart failure that is common to every emergency department, but their severe degree of endothelial dysfunction and heart failure might portend a more potent effect on less desensitized (i.e., less severe heart failure) patient.

Conclusion

Developed during an era of medicine that predated evidence-based practice, nitrates may have been grandfathered in as a cornerstone of management of the acute heart failure (AHF) patient with pulmonary edema. Convincing research demonstrates hemodynamic benefits and some clinical benefits to nitrates, particularly in higher doses and in conjunction with other standard methods of diuresis. However, we do not have a sufficient body of evidence to define their use explicitly or demonstrate their superiority over other afterload reducing or vasodilatory agents. Evidence for how these agents should be used in the emergency department still remains chiefly based on expert opinion.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Storrow AB, Jenkins CA, Self WH, et al. The burden of acute heart failure on U.S. emergency departments. JACC Heart Fail. 2014;2(3):269–77.
2.• Piper S, Mcdonagh T. The role of intravenous vasodilators in acute heart failure management. Eur J Heart Fail. 2014;16(8):827–34. **A succinct review and also discusses vasodilators outside the class of nitrates**
3. Maggioni AP, Anker SD, Dahlström U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12, 440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2013;15(10):1173–84.
4. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):1810–52.
5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016
6.•• VMAC investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA. 2002;287(12):1531–40. **This investigation is the largest RCT involving nitrates and notably placebo.**
7. Levy P, Compton S, Welch R, et al. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. Ann Emerg Med. 2007;50(2):144–52.
8. Collins SP, Storrow AB. Acute heart failure. In: Tintinalli JE, Stapczynski J, Ma O, Yealy DM, Meckler GD, Cline DM, editors. Tintinalli's emergency medicine: a comprehensive study guide, 8e. New York: McGraw-Hill; 2016. http://accessemergencymedicine.mhmedical.com.ezproxyhost.library.tmc.edu/content.aspx?bookid=1658&Sectionid=109428688. Accessed January 12, 2017.
9. Colucci WS Treatment of acute decompensated heart failure: components of therapy. In UpToDate, T.W. Post, S Gottlieb, J Hoekstra (Eds.), available from https://www.uptodate.com/contents/treatment-of-acute-decompensated-heart-failure-components-of-therapy.
10. Wakai A, Mccabe A, Kidney R, et al. Nitrates for acute heart failure syndromes. Cochrane Database Syst Rev. 2013;8:CD005151.
11. Mcmurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803–69.
12. Cohn JN, Mcinnes GT, Shepherd AM. Direct-acting vasodilators. J Clin Hypertens (Greenwich). 2011;13(9):690–2.
13. Chen Z, Zhang J, Stamler JS. Identification of the enzymatic mechanism of nitroglycerin bioactivation. Proc Natl Acad Sci U S A. 2002;99(12):8306–11.
14.•• Münzel T, Steven S, Daiber A. Organic nitrates: update on mechanisms underlying vasodilation, tolerance and endothelial

dysfunction. Vasc Pharmacol. 2014;63(3):105–13. **Provides an excellent and in-depth review of nitrate pharmacology**

15. Den Uil CA, Brugts JJ. Impact of intravenous nitroglycerin in the management of acute decompensated heart failure. Curr Heart Fail Rep. 2015;12(1):87–93.
16. Cotter G, Metzkor E, Kaluski E, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet. 1998;351(9100):389–93.
17. Sharon A, Shpirer I, Kaluski E, et al. High-dose intravenous isosorbide-dinitrate is safer and better than Bi-PAP ventilation combined with conventional treatment for severe pulmonary edema. J Am Coll Cardiol. 2000;36(3):832–7.
18. Levy P, Compton S, Welch R, et al. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. Ann Emerg Med. 2007;50(2):144–52.
19. Wilson SS, Kwiatkowski GM, Millis SR, Purakal JD, Mahajan AP, Levy PD. Use of nitroglycerin by bolus prevents intensive care unit admission in patients with acute hypertensive heart failure. Am J Emerg Med. 2017;35(1):126–31.
20. Uil CA, Lagrand WK, Spronk PE, et al. Low-dose nitroglycerin improves microcirculation in hospitalized patients with acute heart failure. Eur J Heart Fail. 2009;11(4):386–90.
21. Imhof PR, Ott B, Frankhauser P, Chu LC, Hodler J. Difference in nitroglycerin dose-response in the venous and arterial beds. Eur J Clin Pharmacol. 1980;18(6):455–60.
22. Breidthardt T, Noveanu M, Potocki M, et al. Impact of a high-dose nitrate strategy on cardiac stress in acute heart failure: a pilot study. J Intern Med. 2010;267(3):322–30.
23. Smith CJ, Sun D, Hoegler C, Roth BS, Zhang X, Zhao G, Xu X-B, Kobari Y, Pritchard K, Sessa WC, Hintze TH. Reduced gene expression of vascular endothelial NO synthase and cyclooxygenase-1 in heart failure. Circ Res. 1996;78:58–64.
24. Ormerod JO, Arif S, Mukadam M, et al. Short-term intravenous sodium nitrite infusion improves cardiac and pulmonary hemodynamics in heart failure patients. Circ Heart Fail. 2015;8(3):565–71.