**CURRENT OPINION**

# Treating Acute Decompensated Heart Failure in Patients with COVID-19 Using Intravenous Nitroglycerin in 5% Glutathione

Wayne Kaesemeyer[1] · Tatsiana Suvorava[2]

## Abstract

The purpose of this current opinion article is to illustrate a novel approach to the treatment of acute decompensated heart failure (ADHF) in coronavirus disease 2019 (COVID-19) patients. The approach described herein relies on a reformulation of intravenous nitroglycerin in 5% glutathione, itself novel, and is felt to have the potential to not only improve the rate of resolution of ADHF, but also reduce the risk of complications of heart failure seen in patients with COVID-19.

## Key Points

This paper continues our approach to treating coronavirus disease 2019 (COVID-19) as a disease of the vascular endothelium with a focus on heart failure.

We propose studying the use of intravenous (IV) glyceryl trinitrate (GTN) in 5% glutathione to reduce the need for mechanical ventilation in heart failure patients who are initially stable and newly diagnosed with COVID-19.

Prevention of superoxide-mediated tolerance in the use of IV GTN for treatment of heart failure patients with COVID-19 may reduce the risk of mortality from decompensation of heart failure and COVID-19.

The mortality of coronavirus disease 2019 (COVID-19) in patients with heart failure has recently been found to be 41% [1]. Of those heart failure patients requiring hospitalization for treatment of COVID-19, 33% develop acute decompensated heart failure (ADHF) [1]. Mortality in this subgroup has been shown to be almost 50% [2]. Furthermore, it is anticipated that the incidence of ADHF may significantly increase [3].

Conditions involving endothelial dysfunction predispose patients to developing COVID-19. Targeting the vascular endothelium, including the use of glutathione (GSH), has been proposed as part of the overall strategy for treating patients with COVID-19 [4]. Endothelial dysfunction underlies heart failure of all types, including ADHF. Furthermore, patients with reduced left ventricular function, the most common cause of ADHF, have an increased risk of becoming infected with COVID-19 [5].

Guidelines for treating ADHF recommend adding intravenous (IV) glyceryl trinitrate (GTN) to diuretics for rapid improvement in congestive symptoms [6]. One of the limitations of using IV GTN is the rapid development of tolerance.

Tolerance is generally defined as gradual loss of hemodynamic or anti-anginal effects with sustained GTN therapy. With the use of IV GTN in the treatment of ADHF, tolerance refers to loss of hemodynamic effect over a 24-h period as measured by pulmonary capillary wedge pressure [7]. There have been multiple theories to explain tolerance. These include impaired biotransformation of GTN [8, 9], changes of neurohumoral activity [10], phosphodiesterase activity upregulation with reduced cyclic guanosine monophosphate (cGMP) levels [11], loss of soluble guanylate cyclase (sGC) responsiveness to nitric oxide (NO) [12], depletion of sulfhydryl groups [13], and most recently, generation of free radicals [14, 15].

The scope of this paper is limited to GTN, which is a distinct chemical entity, different from all the other nitrates. A detailed review of the subject of nitrate tolerance is beyond

✉ Wayne Kaesemeyer
kaehtn007@yahoo.com

1 Augusta Hypertension PC, 108 Tharrington Drive, Chapel Hill, NC, USA

2 Institute of Pharmacology and Clinical Pharmacology, University Hospital, Duesseldorf, Germany

the scope of this paper, and the reader is referred to [16] for more on this issue. Furthermore, the focus of this approach for using IV GTN for treatment of ADHF in patients with COVID-19 is the reduction in the generation of superoxide and related free radicals, the most recent mechanism for explaining tolerance [17].

It has been demonstrated that the vasodilator actions of GTN are potentiated by GSH when both GTN and GSH are administered simultaneously in human coronary arteries [18]. In 1987, Packer et al. reported that tolerance to GTN, seen in the treatment of heart failure, can be prevented by the GSH prodrug *N*-acetylcysteine [13]. GSH has also been shown to normalize rheologic responses to GTN in patients with diabetes [19]. Another approach to providing GSH to GTN, upregulating glutathione *S* transferase (GST), has also been shown to minimize or eliminate tolerance [20]. So, it appears that tolerance is benefitted regardless of whether GSH is provided exogenously or endogenously. The finding of benefit from targeting GST seems to reinforce the significance of the role of superoxide in the overall problem of tolerance.

Tolerance induced by GTN has been shown to result from superoxide generation from mitochondrial complex I as a result of depletion of GSH. And GSH was found to reverse both superoxide generation by complex I and tolerance [21]. This is illustrated in Fig. 1. The role of complex I, concomitantly with endothelial nitric oxide synthase (eNOS), itself an independent site of superoxide synthesis [22], in

the overall process leading to tolerance is summarized as follows:

1. Prolonged treatment with GTN leads to inhibition of mitochondrial complex I [21]. This results in superoxide production by complex I (first radicals). Afterwards, GSH is oxidized to oxidized glutathione disulfide (GSSG), which depletes GSH. Depletion of GSH leads to further superoxide/reactive oxygen species (ROS) generation.

2. Superoxide and superoxide-generated reactive oxygen and nitrogen species (peroxynitrite and $H_2O_2$) induce GSH suppressible tolerance by inhibition of aldehyde dehydrogenase-2 (ALDH-2) [16, 21, 23–26].

3. Superoxide-generated peroxynitrite and $H_2O_2$ upregulate arginase-2 [27].

4. Upregulated arginase-2 depletes L-arginine at the site of activity of eNOS, leading to further superoxide production [22] and tolerance [17], which can be reversed by inhibiting arginase and supplementing L-arginine [28].

5. Superoxide and peroxynitrite from GTN in conditions of tolerance can lead to activation of protein kinase C and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which further amplifies superoxide generation and tolerance [17, 25].

6. Total NO from GSH- and L-arginine-supplemented GTN is a combination of NO from bioconversion plus



**Fig. 1** Schematic summary of the overall process leading to tolerance to GTN. Points 1–7: summary items (see in text). *ALDH-2* aldehyde dehydrogenase-2, *ARG-2* arginase-2, *EC* endothelial cells, *EDNO•* endothelium-derived NO, *eNOS* endothelial nitric oxide synthase, *GSH* glutathione, *GTN* glyceryl trinitrate, *NADPH* nicotinamide adenine dinucleotide phosphate, *PK C* protein kinase C, *RNS* reactive nitrogen species, *ROS* reactive oxygen species, *unc eNOS* uncoupled eNOS, *VSMC* vascular smooth muscle cells
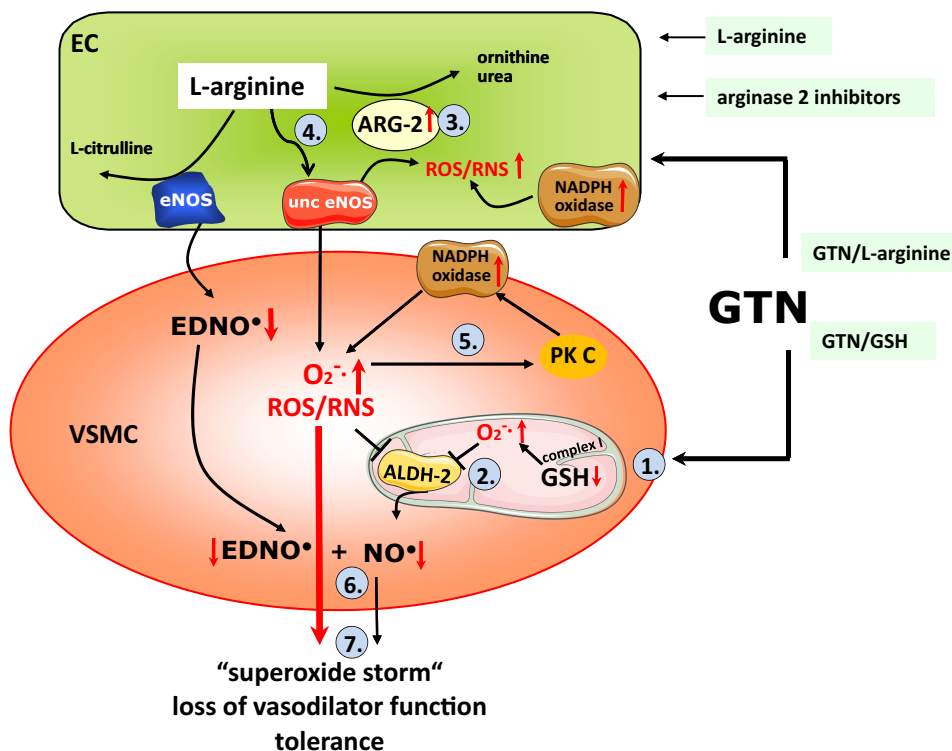
endothelium-derived NO (EDNO) from eNOS [9, 27, 29].

7. Unsupplemented GTN administration results in initial NO from bioconversion followed by superoxide and peroxynitrite formation [30]. On prolonged administration, tolerance develops with loss of vasodilator function. This overall process can be viewed as a "superoxide storm."

So, it appears that what previously has been termed the "sulfhydryl-depletion hypothesis" [31] might now better be referred to as the "glutathione-depletion hypothesis."

Vasodilation from GTN continuously supplemented with GSH and L-arginine is anticipated to be maintained indefinitely, albeit somewhat less than that seen with a first sublingual tablet. However, with the elimination of superoxide seen currently with IV GTN in dextrose, the dose of GTN required in the treatment of ADHF is expected to be considerably reduced using IV GTN in 5% GSH.

Vasodilator function on long-term administration may still be subject to other processes that lead to tolerance. These include downregulation of sGC and upregulation of phosphodiesterase activity. But neurohumoral activation, impaired biotranformation to NO, and sulfhydryl depletion will largely be eliminated.

Superoxide production as part of tolerance with the use of IV GTN not only limits its effectiveness in the treatment of ADHF, but it also predisposes patients to becoming infected with COVID-19 and its complications [4]. This is because superoxide from endothelial dysfunction increases the ratio of angiotensin-converting enzyme (ACE) to ACE2 and thereby increases the likelihood of ACE2 becoming a binding protein for the virus causing COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]. This, then, additionally explains the rationale for the reformulation described below.

Currently, GTN for IV administration is formulated in 5% dextrose, as shown in Table 1A, along with its proposed reformulation (shown in Table 1B).

Before a product can be approved for sale by the Food and Drug Administration (FDA), it has to be shown that GTN levels are maintained for 18 months. For GTN solutions in L-arginine alone, this requirement has been met previously (data not shown but available). Regarding GSH, it, theoretically, if stored exposed to air, could undergo oxidation to GSSG. But storage in sealed glass bottles is felt to eliminate this concern. However, for commercial sale, this is another 18-month study that needs to be performed. But for immediate use for treating or preventing ADHF, GSH stability is not a concern.

As in the case of dextrose, both GSH and arginine are non-xenobiotics referred to as generally regarded as safe (GRAS) agents. Therefore, animal toxicology studies are likely unnecessary (Kaesemeyer, personal communication, 1998, US FDA). And there are studies suggesting it is not

**Table 1** Current reformulation of nitroglycerin in dextrose 5% (A) and proposed reformulation of nitroglycerin in GSH (B)

(A) Nitroglycerin in dextrose 5%

|  | Composition | | Osmolarity (mOsmol/L) (calc) | pH |
|---|---|---|---|---|
|  | Nitroglycerin (µg/mL) | Dextrose hydrous, USP (g/L) |  |  |
| 25 mg nitroglycerin in 5% dextrose injection | 100 | 50 | 428 | 4.0 (3.0–5.0) |
| 50 mg nitroglycerin in 5% dextrose injection | 200 | 50 | 440 | 4.0 (3.0–5.0) |
| 100 mg nitroglycerin in 5% dextrose injection | 400 | 50 | 465 | 4.0 (3.0–5.0) |

(B) Proposed reformulation of nitroglycerin in GSH 5%

|  | Nitroglycerin (µg/mL) | GSH[a], USP (g/L) | Osmolarity (mOsmol/L) (calc) | pH |
|---|---|---|---|---|
| 25 mg nitroglycerin in 5% GSH injection | 100 | 50 | 428 | 4.0 (3.0–5.0) |
| 50 mg nitroglycerin in 5% GSH injection | 200 | 50 | 440 | 4.0 (3.0–5.0) |
| 100 mg nitroglycerin in 5% GSH injection | 400 | 50 | 465 | 4.0 (3.0–5.0) |

*GSH* glutathione, *GTN* glyceryl trinitrate, *USP* United States Pharmacopeia

[a]Buffered to pH 3–5 with L-arginine. This reformulation involves dissolving 50 g GSH (USP grade) in 800 mL of water. Once this dissolves, 20 g of L-arginine are added and dissolved. Next GTN concentrate, 5 mg/mL, is added (20, 40, or 80 mL) as indicated in Table 1B. The total volume is increased to 1 L. The pH is checked to be sure it is in the range of 3–5. If not, it can be further adjusted by adding NaOH or HCl. Once this is complete, the solution is passed through a 22-µm Millipore filter to insure it is free of impurities and bacteria. Then it is transferred to airtight sealed glass bottles, generally 250 mL. This is referred to as "sterile fill," and it is a process that can be done by compounding pharmacies. It is also suitable for commercial product manufacture (Alcami, personal communication, 2020). At the pH of 3–5, GTN is stable indefinitely. At pHs below 3, GTN undergoes slow degradation by one chemical reaction, and at pH greater than 5, it slowly degrades by a different reaction

only safe but desirable for use in pregnancy, especially in pre-eclampsia [32].

For treating ADHF in COVID-19 patients using IV GTN 200 μg/mL 5% GSH, the dosing regimen would be 1–2 mL/h initially (5 μg/min or 0.075 μg/kg/min) with an increase of 1–2 mL/h every 5 min for relief of dyspnea or systolic blood pressure of 100–110 mmHg. An important point to be made here is that, as with IV GTN in 5% dextrose, IV GTN in 5% GSH can be given on top of background medications without concern for drug–drug interactions requiring discontinuation of some background drugs, i.e., ACE inhibitors.

Regarding the above discussion of GSH side effects, as with IV GTN in 5% dextrose, the only drug being administered with IV GTN in 5% GSH is GTN. GSH is supplied to support GTN's requirement for suppressing superoxide production. Moreover, regarding L-arginine, it was used for diagnosis of adult growth hormone deficiency [33]. This would be far more than the amount that would be used in the formulation of Table 1B.

Finally, it should be noted that a considerable percentage of ADHF patients have type II diabetes. Mitochondrial GSH levels are depressed in diabetics [34], and hyperglycemia further aggravates GSH depletion [34]. Moreover, recent evidence indicates glucose enhanced SARS-CoV-2 viral load and mRNA expression of pro-inflammatory cytokines and type I/III interferons in monocytes in a dose-dependent manner. These effects of glucose were found to be dependent on mitochondrial reactive oxygen species (mtROS) and hypoxia-inducible factor 1-alpha (HIF1α) [35]. Therefore, eliminating dextrose from IV GTN as in Table 1B would seem desirable.

Similarly, GSH can become depleted under conditions of oxidative stress such as those seen in ischemia. This is another reason for supplementing IV GTN with GSH used in the place of dextrose.

In conclusion, published studies suggest that superoxide production in GTN tolerance is both GSH and L-arginine dependent. The purpose of replacing dextrose with GSH is to suppress superoxide production from continuous IV GTN administration. This is to minimize or eliminate the development of tolerance mediated by superoxide and thereby improve overall function of the vascular endothelium of COVID-19 patients with heart failure.

We feel that a clinical trial of IV GTN in 5% GSH is needed. We would like to study patients with heart failure with reduced ejection fraction hospitalized for the treatment of newly diagnosed COVID-19. At the time of admission, heart failure would be considered compensated and patients could be managed on a telemetry unit. COVID-19 would be treated at the discretion of the admitting physician. In addition, patients would be randomized to treatment with IV GTN in dextrose versus IV GTN in GSH, both titrated as tolerated to a systolic blood pressure of 100–110 mmHg. The

primary endpoint would be the need for mechanical ventilation and transfer to a coronary care or an intensive care unit for treatment of decompensation of heart failure or pneumonia with acute respiratory distress syndrome (ARDS). Other complications [4] would be secondary endpoints. These would include biomarkers (troponins, N-terminal prohormone of brain natriuretic peptide [NT-proBNP], C-reactive protein [CRP], etc.), changes in global longitudinal strain on echocardiogram, and the need for vasopressors to treat endotoxic shock.

Seeing a benefit of IV GTN/GSH versus IV GTN in this very high-risk group of patients would be significant and may justify further studies of IV GTN in 5% GSH. This could include a larger trial involving ADHF in patients without COVID-19.

Overall, we believe this approach to target superoxide from GTN and its effects on the vascular endothelium may help to simultaneously reduce the risk of complications from both heart failure and COVID-19.

## Declarations

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