

Higenamine as a Potential Pharmacologic Stress Agent in the Detection of Coronary Artery Disease

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ABSTRACT

Myocardial perfusion imaging (MPI) is valuable for the diagnosis, prognosis, and management of coronary artery disease (CAD). The most commonly used pharmacologic stress agents at present are vasodilators and adrenergic agents. However, these agents have contraindications and may cause adverse effects in some patients. Thus, other stress agents feasible for more patients are required. Higenamine (HG) is a β -adrenergic receptor agonist currently approved for clinical trials as a stress agent for myocardial infarction. It also has a promising value in MPI for the detection of CAD in preclinical and clinical studies. This review summarizes the application of HG on MPI, including its mechanism of action, stress protocol, efficacy, and safety.

Key words: coronary artery disease; higenamine; myocardial perfusion imaging; stress agent

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death worldwide^[1]. Myocardial perfusion imaging (MPI) is a non-invasive modality used in the detection, stratification, and management of CAD^[2]. Although exercise stress is recommended as the first choice for MPI whenever possible, many people are not suitable for exercise stress due to aging and cardiovascular risk factors such as obesity and diabetes^[3, 4]. Actually, more than half of the stress MPI tests are performed with pharmacological agents instead of exercise^[5].

Two categories of pharmacological stress agents are available: vasodilators and adrenergic agents.

Adenosine, dipyridamole, and regadenoson are the most commonly used vasodilators in MPI^[6, 7]. However, vasodilators exert drug-induced constrictions such as asthma, chronic obstructive pulmonary disease, and atrioventricular block, resulting in adverse events^[8]. Dobutamine, one of the few adrenergic agents, has been recommended for patients who have contraindications for vasodilators^[9, 10]. However, dobutamine stress MPI is not recommended in patients with severe hypertension^[11]. Thus, the development of effective alternative tachycardia agents that are feasible for more patients is needed.

Higenamine (HG) is a benzyltetrahydroisoquinoline alkaloid with a full chemical name of 1-(4'-hydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, which was initially isolated from the roots of *Aconitum* by Kosuge *et al.* in 1976^[12]. At present, it can be produced by chemical synthesis as a form of chloride salt with a white powder appearance and relatively good solubility. Although HG possesses a

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far-ranging pharmacological function^[13], it is currently only approved for clinical trials as a pharmacological stress agent for myocardial infarction^[14]. HG is a positive inotropic agent that can directly stimulate the β -adrenergic receptor (β -AR), with a short duration of action^[15]. This review article discusses the unique features and mechanism of action of HG as a stress agent and summarizes the findings of pre-clinical and clinical studies on the value of HG in MPI.

PHARMACOLOGICAL MECHANISMS OF HIGENAMINE AS A STRESS AGENT

Although three vasodilators (i.e., adenosine, dipyridamole, and regadenoson) can be used for MPI, few adrenergic agents except dobutamine are recommended for patients who have contraindications for vasodilators. Dobutamine exerts drug-induced constrictions; thus, it is not recommended in patients with severe hypertension. HG may be an inotropic option for MPI. It mainly contains cardiogenic components from the aconite roots^[16], and the catecholamine moiety gives HG a dobutamine-like effect, making its use feasible in MPI (**Fig. 1**). HG is a β -AR exerting a direct β_1 and β_2 -AR stimulation^[17, 18]. HG can cause a dose-dependent increase in heart rate and myocardial contractility, consequently increasing the regional myocardial blood flow as a result of the positive inotropic and chronotropic response through the activation of β -AR. HG stress MPI evaluates CAD by detecting the discrepancy of blood flow between the normal and abnormal myocardial regions.

HG binds to β -AR with an affinity of 6.35 and stimulates β -arrestin-mediated signaling^[19]. β -arrestin-dependent ERK1/2 activation is a unique signaling profile generally associated with decreased apoptosis and increased survival of the cardiovascular cells^[20], which may be responsible for the reduced damage and

side effects during the MPI experiment. Besides, HG is a novel α_1 adrenoceptor antagonist that contributes to its hypotensive effect^[21]. Therefore, the pharmacology of HG indicates that HG stress MPI is feasible for patients with severe hypertension, for whom dobutamine is contraindicated.

PRECLINICAL STUDIES ON HIGENAMINE AS A STRESS AGENT

Preclinical studies in animal models demonstrated the effectiveness and safety of HG as a stress agent for MPI. Chen *et al.*^[22] established dog models to evaluate the hemodynamic effect of HG. They used a solid-state pressure gauge in left ventricular (LV) apex to measure the LV systolic pressure and its first derivative (LV dp/dt_{max}) during HG infusion ($5 \mu\text{g}\cdot\text{kg}^{-1}$). HG increased left ventricular systolic pressure (LVSP) and dp/dt_{max} by 92.5% and 97.07%, respectively, while the decrease in mean arterial blood pressure and systemic vascular resistance was 14 mm Hg and 39.28%, respectively. Liu *et al.*^[23] compared the hemodynamic effects of HG versus dobutamine to evaluate whether HG could be used as a cardiac pharmacological stress agent in dog models. HG increased the heart rate in a dose-dependent manner. The infusion of both HG ($1-4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and dobutamine ($5-10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) at 5 min interval induced a similar increase in heart rate, myocardial oxygen consumption, cardiac output, and LV ejection fraction in a dose-dependent manner. Similar results were observed by Zhang *et al.* in dog models^[24]. Coronary blood flow was increased by 68% in HG ($4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) group while coronary blood flow was only increased by 48% in dobutamine ($20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) group^[24]. Importantly, the effects of HG and dobutamine at the same doses on the blood pressure were significantly different. Dobutamine slightly increased systolic blood pressure (SBP) and diastolic blood pressure (DBP); in contrast, HG did not affect SBP and induced a slight decrease in DBP^[24]. These results in dog models demonstrated that HG can be used in pharmacological stress tests as well as an alternative agent to dobutamine under appropriate circumstances.

Another study explored the use of HG as a new agent for pharmacological stress test in the detection of CAD in pig models by radionuclide MPI^[25]. The quality of the images induced by HG ($4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) or dobutamine ($40 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was comparable.

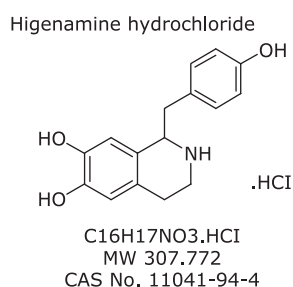


Figure 1. Chemical structure of higenamine hydrochloride
MW: molecular weight

Imaging scores (9.9 ± 8.5 vs. 9.4 ± 8.6) and defect severity ($68\% \pm 12\%$ vs. $68\% \pm 15\%$) between HG and dobutamine (DB) stress tests were not significantly different^[25]. However, HG differed from dobutamine in its effect on coronary resistance, since it decreased the coronary vascular resistance more significantly than dobutamine^[26]. Zhang *et al.*^[24] found similar results in dog models by intravenous injection of HG. Besides, the heart rate response induced by HG is more rapid than that induced by dobutamine. HG increased heart rate by 36 bpm at 3 min after infusion while dobutamine increased it by only 21 bpm^[25]. HG was well tolerated by animals even at an extraordinarily high dose despite its remarkable effect on tachycardic induction at a low dose ($22.5 \mu\text{g}\cdot\text{kg}^{-1}$). The LD_{50} of HG was approximately $50 \text{ mg}\cdot\text{kg}^{-1}$ for injection in mice^[27]. An animal experiment investigating the tolerability and safety of HG revealed no abnormal electrocardiographic finding or death at the increasing doses from $1 \mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$ to $500 \mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$, with the infusion time being 3 min for each dose. After the treatment, the heart rate and blood pressure of these dogs returned back in approximately 100 minutes^[24]. These preclinical results confirmed the safety of HG and, more importantly, suggested the potential advantages of HG over dobutamine.

CLINICAL STUDIES ON HIGENAMINE

Protocols, pharmacokinetics, and pharmacodynamics

The protocols for the use of HG are similar to those of dobutamine. The intravenous infusion of HG should be performed using a pump. HG is administered at increasing doses of $0.5 \mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$, $1 \mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$, $2 \mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$, and $4 \mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$, each for 3 min, while dobutamine should be intravenously infused at a dose of $5 - 10 \mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$ and increased to 20, 30, and $40 \mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$ every 3 min^[28, 29].

A phase I study using the above protocol revealed desirable pharmacokinetic and pharmacodynamic characteristics of HG in volunteers^[29]. The pharmacokinetics of HG was successfully described using a two-compartment model with nonlinear clearance. The heart rates were related to the plasma drug concentrations in the pharmacodynamic model. A total of 94% of HG was cleared from the body 30 min after its administration, and meanwhile the heart rate returned to the baseline. The half-life of HG was approximately 8 min. HG had a distribution volume of 18.7 L and 43.0 L (at

steady state). The clearance rate of HG was $3.8 \text{ L}\cdot\text{min}^{-1}$ at the peak concentrations ranging from 15.1 to $44.0 \text{ ng}\cdot\text{mL}^{-1}$. HG was cleared mainly through the liver instead of kidney. Only 9.3% of the HG was excreted through the kidney within 8 h. However, additional studies should be carried out in future, especially in elderly people and/or obese patients.

Changes in heart rate and blood pressure

The use of HG in MPI is based on its inotropic effect of strengthening the force of the heartbeat to reach the targeted heart rate. This drug is able to induce a rapid and significant increase of the heart rate within 2 min during drug infusion. The average maximum heart rate induced by HG in patients at the dose of $22.5 \mu\text{g}\cdot\text{kg}^{-1}$ was 126 bpm^[29]. The heart rate of the patients returned to the baseline 30 min after the end of drug administration, representing one of the significant advantages of HG as a stress agent. Another study investigated the tolerability of HG in 32 healthy volunteers: they were divided into four groups receiving HG infusion at the doses of 0.5, 1.0, 2.0, and $4.0 \mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$ ^[30], with each dose lasting 6 min. The heart rate increases in a dose-dependent manner after intravenous administration of HG. In addition, HG significantly increased the myocardial oxygen consumption, with the maximum increase up to $3,400 \text{ mL}\cdot\text{min}^{-1}$, as observed in patients^[31]. However, HG was associated with minor effects on blood pressure despite its remarkable cardiac impact. The SBP of patients was not significantly affected by HG; DBP slightly decreased but returned to the baseline within 5 min after the end of infusion^[29, 31].

Myocardial perfusion imaging using higenamine

The current clinical studies on HG as a stress agent are successful^[31-37]. The effectiveness in diagnosing CAD is based on the results of coronary angiography. The diagnostic accuracy of HG is expressed by its sensitivity and specificity, as in other pharmacological MPI tests. In these studies, coronary arteriography was guided by the results of the stress test. The reported sensitivity, specificity, and accuracy for each of the available studies^[31-37] are shown in **Table 1**. These studies showed that the sensitivity of HG at the increased doses up to $4.0 \mu\text{g}\cdot\text{kg}^{-1}\text{min}^{-1}$ for the detection of diseases was similar to or slightly lower than the sensitivity of adenosine^[32]. The similarity in the rates of HG with adenosine is more than 90% by visual and quantitative analyses.

However, a larger multicentric study is needed to clearly define the sensitivity of HG in patients with CAD.

A total of 109 patients with confirmed or suspected myocardial ischemia were enrolled in a phase II trial study, and stress was induced by the infusion of HG at increasing doses up to $4.0 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to perform MPI, which was compared with adenosine stress test in the same patients^[34, 37]. These patients were randomly divided and subjected to sequential MPIs with HG or adenosine on different days. The MPI results revealed the following diagnostic values of HG versus adenosine injection: sensitivity (56.1% vs. 52.6%), specificity (78.8% vs. 82.7%), accuracy (67.0% vs. 67.0%), positive predictive value (74.4% vs. 76.9%), and negative predictive value (62.1% vs. 61.4%). Thus, as a stress agent, HG is similar to adenosine in the diagnosis of CAD. Moreover, the Kappa values of HG in detecting the left anterior descending, left circumflex, and right coronary arteries were 0.891, 0.842, and 0.887, respectively, in good agreement with those of adenosine. Thus, HG is comparable with adenosine in the detection of the heart areas with a reduced flow. Similar results were also observed by Tian Rui *et al*^[32].

To date, no human clinical studies have been performed to compare HG with dobutamine. The animal study conducted by Zheng *et al*. showed an excellent agreement of HG- with dobutamine-based stress MPI in the detection of CAD, with a sensitivity of 92%^[25]. Therefore, comparisons between these two drugs in humans should be performed in future clinical trials.

Safety and side effects

HG had good safety and tolerability profiles both in healthy people and CAD patients administered at in-

creasing doses of $0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, each for 3 min. Approximately 70% of patients experienced adverse reactions during infusion of HG^[32, 34, 37]. Nevertheless, adverse reactions associated with HG are usually mild, and they resolve in 10 min - 20 min after the infusion and may vary from person to person. The most common side effects are palpitation, chest congestion, chest pain, and dizziness^[31, 33, 34]. A phase I study revealed that two of the 10 subjects reported one adverse event each^[29]. Approximately 16% of the patients experienced dizziness, as reported in another study that enrolled 32 healthy people^[30]. Two patients experienced nausea and ventricular premature beat, respectively^[30]. No life-threatening side effect has been reported. No study has reported an HG stress MPI that is unable to diagnose a disease due to an insufficient hemodynamic response or limiting side effects. So far, the clinical adverse effects of HG appear to be tolerable. However, the percentage of each side reaction needs to be further clarified.

POTENTIAL USE IN SPECIAL POPULATION

HG has some excellent advantages to be potentially used among special subpopulations due to its unique characteristics. Two examples are listed below.

Respiratory diseases

Some stress agents like adenosine and dobutamine are contraindicated in patients with respiratory diseases like asthma^[38, 39] because they tend to induce bronchospasm. HG can be of great value for such patients^[40] since HG is a potent β_2 -AR agonist ($p\text{Ki}=6.435$) and β_2 -AR agonists induce the relaxation of the airway smooth

Table 1. Diagnostic accuracy of higenamine stress myocardial imaging reported in 6 studies

Year	Author	Tracer	Analysis	Sample size	Age (y/d) Mean	Male (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Negative predictive value (%)
2012	Zhou W ^[31]	Tc-99m	SPECT	62	61	65	65.5	84.9	75.8	79.2	73.7
2012	Tian R ^[32]	Tc-99m	SPECT	128	58	58	56.0	78	67	75	62
2012	Cao Y ^[33]	Tc-99m	SPECT	62	65	63	57.9	91.7	71.0	91.7	57.9
2014	Du YR ^[34]	Tc-99m	SPECT	109	58	54	56.1	78.8	67.0	74.4	62.1
2015	Mi HZ ^[35]	Tc-99m	SPECT	60	56	60	69.0	80.6	75.0	76.9	73.5
2015	Sun Y ^[36]	Tc-99m	SPECT	100	57	56	76.5	93.8	93.8	76.5	32.0
2018	Bai H ^[37]	/	Echocardiography	90	49	57	28.9	89.7	57.1	76.5	47.8

muscles to treat various respiratory diseases^[41]. HG may relax tracheal smooth muscles, as indicated by its potent dose-dependent effects *in vitro*. Its hypodermic injection at the dose of 2 mg·kg⁻¹ in a dog model inhibits the asthma induced by histamine^[42, 43]. Besides, HG is a main component of some traditional Chinese medicine [such as Radix Aconit Lateralis Preparata (RALP), and Gnetumparvifolium (Warb.) G.Y. Cheng] in treating bronchoconstriction diseases^[44]. Theoretically, HG can be safely administered in patients with bronchoconstriction.

Atrioventricular block or sinus node dysfunction

The diagnosis of CAD is challenging in patients with atrioventricular block or sinus node dysfunction^[45], and HG has demonstrated advantages over other pharmacological agents for these subgroups of patients. HG administered via infusion at the dose of 40 µg·kg⁻¹ was used to treat bradyarrhythmia in sick sinus syndrome and atrioventricular block^[46-49]. HG shortens the sinus node recovery time or corrects it as well as remarkably shortens the total sinoatrial conduction time and sinus cycle length^[50, 51]. Accordingly, HG may be safely used in patients with atrioventricular block or sinus node dysfunction.

SUMMARY AND PERSPECTIVES

With fast clearance and good safety profile, HG is a promising stress agent in MPI, providing a new choice for patients. With its unique pharmacologic activation profiles, HG confers some advantages over other common pharmacological stress agents and meanwhile is indispensable for patients with respiratory diseases or atrioventricular block. However, the value of HG has been assessed in only a small number of patients, and the clinical efficacy of HG *versus* other current stress agents is not convincing. In future, larger studies are warranted to further elucidate its clinical strength and weakness.

Conflict of interest

No competing interests disclosed.

Authors' contributions

Conceptualization: Zhang NN, Li ZJ, and Zhu HB; original draft preparation: Zhang NN; review and editing: Li ZJ and Zhu HB. All authors have read and agreed to the final version of the manuscript.

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综述

去甲乌药碱：一种潜在的冠心病诊断心肌负荷药物

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摘要

心肌灌注显像在冠心病的诊断、预后和管理中具有重要价值。当前，血管扩张剂和肾上腺素剂是最常见的心肌负荷药物。然而，这些药物在部分病人中的应用有限制，并且有多种副反应。因而，有必要开发可以在更多病人中应用的心肌负荷药物。去甲乌药碱是一种 β 受体激动剂，被批准作为心肌负荷药物应用于心肌缺血的诊断。因其正性肌力作用，去甲乌药碱有望成为用于冠心病诊断的心肌灌注显像负荷药物。本综述总结了去甲乌药碱在心肌灌注显像中的应用，包括其作用机制、给药方式、有效性及安全性。

关键词：去甲乌药碱；心肌灌注显像；负荷药物；冠状动脉疾病

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