

# Nicotine and Nicotine Replacement Therapy Use During Myocardial Perfusion Imaging

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**Background:** Myocardial perfusion imaging (MPI) is commonly used to assess the presence and severity of coronary artery disease (CAD). A radiopharmaceutical is used before and after patients undergo either exercise-induced stress via a treadmill or medication-induced stress. While certain therapies that are known to influence the accuracy of results are avoided prior to conducting MPI, it is currently unknown whether nicotine and nicotine replacement therapy (NRT) should be avoided, even though they may have significant effects on coronary circulation.

**Observations:** Nicotine has been demonstrated to have both vasoconstrictive and vasodilatory properties. However, in patients with underlying CAD, vasoconstrictive properties ap-

pear to predominate and can allow the disease to appear more severe than it is during MPI. Similarly, NRT products may cause vasoconstriction but to a lesser degree given the lower concentration of nicotine present. Due to the lack of robust studies, the clinical impact of these findings on clinician diagnosis and patient management remains unclear.

**Conclusions:** Based on the available data, nicotine and NRT should ideally be avoided prior to MPI. The specific time frame in which they would be stopped before conducting MPI differs based on the pharmacokinetics of each product. More studies are needed to analyze the impact of nicotine and NRT on the accuracy of MPI using medication.

Chest pain is one of the most common concerns in patients presenting to the emergency department in the United States, accounting for approximately 7.6 million visits annually.<sup>1</sup> Given the high mortality rate associated with acute coronary syndromes, prompt evaluation of chest pain is essential.<sup>2</sup> Even in mild cases, recognition of newly onset or worsening coronary artery disease (CAD) is crucial to ensure that patients receive optimal medication therapy.

In symptomatic patients with risk factors for CAD, such as advanced age, hypertension, hyperlipidemia, obesity, and diabetes mellitus, myocardial perfusion imaging (MPI) is frequently used as a modality to assess the presence, location, and severity of ischemic or infarcted myocardium.<sup>2</sup> MPI requires administration of a radiopharmaceutical before and after the patient undergoes a form of stress.<sup>2</sup> This radiopharmaceutical is then detected in the myocardium with a nuclear camera, and images are obtained of the heart to assess myocardial blood flow.<sup>2</sup>

MPI can be performed using exercise-induced stress via a treadmill, or medication-induced stress (Table 1). In both strategies, healthy coronary arteries dilate to provide the myocardium with more blood flow to meet the increasing myocardial oxygen demand during this period of stress. While healthy vessels are able to dilate appropriately, coronary arteries with flow-limiting stenoses

are unable to dilate to the same extent in response to stress.<sup>2</sup> Because radioactive isotope uptake by the myocardium is directly related to arterial blood flow, MPI is able to demonstrate a mismatch in coronary blood flow between healthy and diseased coronary arteries indicated by differences in radioisotope uptake.<sup>2</sup> The presence of such a mismatch, in conjunction with clinical history, potentially suggests the presence of CAD.

Prior to conducting MPI with a medication, certain substances should be avoided. For instance, methylxanthines, such as caffeine, aminophylline, and theophylline, antagonize adenosine receptors and can have major drug interactions with regadenoson, adenosine, and dipyridamole. Therefore, it is advised that these substances be stopped for at least 12 hours before testing.<sup>3</sup> In some cases, other medications that can affect coronary blood flow, such as long-acting nitrates,  $\beta$ -blockers, and calcium channel blockers, are recommended to be avoided for 12 to 48 hours in order to obtain the most accurate depiction of underlying coronary disease.<sup>4</sup>

Because nicotine and nicotine replacement therapy (NRT) may have substantial effects on coronary circulation, a current area of controversy is whether these should be stopped prior to the use of a stress-inducing medication during MPI. To date, no formal drug interaction studies have been conducted between nicotine and regadenoson.<sup>5</sup>

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*Fed Pract.* 2022;39(1).  
Published January 12.  
doi:10.12788/fp.0217

**TABLE 1** Pharmacologic Agents Used for Myocardial Perfusion Imaging

Agents	Mechanisms of Action	Doses and Administrations	Half-life	Adverse Effects	Contraindications
Regadenoson <sup>5</sup>	Adenosine A <sub>2A</sub> receptor agonist (subtype-selective, potent, and low affinity agonist at this receptor)	0.4 mg IV bolus over 10 min	1-4 min	Chest pain, cardiac dysrhythmias, increased heart rate, headache, flushing, nausea, dyspnea	2nd- or 3rd-degree atrioventricular block or sinus node dysfunction without pacemaker, bronchospasm, hypotension
Adenosine <sup>25</sup>	Nonselective adenosine A <sub>1</sub> and A <sub>2</sub> receptor agonist	140 mcg/kg/min IV infusion over 6 min	< 10 sec	Chest pain, flushing, headache, nausea, dizziness, dyspnea, atrioventricular block	Active bronchospasm or reactive airway disease, 2nd- or 3rd-degree atrioventricular block, sinus node disease, hypotension
Dipyridamole <sup>26</sup>	Inhibits the intracellular uptake and deamination of adenosine, resulting in increased adenosine concentrations to act on A <sub>1</sub> and A <sub>2</sub> receptors	0.142 mg/kg/min IV over 4 min (0.57 mg/kg total, max 60 mg)	Similar to adenosine	Chest pain, hypotension, flushing, headache, nausea, dizziness, dyspnea	Active bronchospasm or reactive airway disease, 2nd- or 3rd-degree atrioventricular block
Dobutamine <sup>27</sup>	Direct B <sub>1</sub> and B <sub>2</sub> receptor stimulation	5-10 mcg/kg/min, increased at 3 min intervals to 20-40 mcg/kg/min	About 2 min	Palpitations, chest pain, headache, flushing, dyspnea, ventricular arrhythmias	Aortic stenosis, recent myocardial infarction, unstable angina, prior history of ventricular arrhythmias

Similarly, the ADVANCE MPI 2 Trial, which led to the US Food and Drug Administration approval of regadenoson, did not specify restrictions on the use of nicotine prior to stress testing in the protocol.<sup>6</sup> However, as this trial was multicenter, investigators admit that individual study sites could have had their own restrictions on the use of nicotine prior to stress testing with regadenoson, but this information was not collected.<sup>6</sup> The current review focuses on how the simultaneous use of nicotine or NRT during MPI with pharmacologic agents, such as regadenoson, may affect the accuracy of imaging results and the clinical impact of this interaction.

#### Nicotine Coronary Artery Effect

It is well documented that long-term cigarette smoking is a major risk factor for CAD.<sup>7</sup> Compared with nonsmokers, cigarette smokers experience 2 times greater risk of morbidity and mortality from ischemic heart disease.<sup>7</sup> There are several mechanisms by which nicotine induces damage to the myocardium (Figure). Nicotine has direct effects on both the sympathetic nervous system (SNS) and myocardial endothelium.<sup>8</sup> Together, these factors result in reduced coronary blood flow, leading to less oxygen supply to meet an increased oxygen demand, resulting in myocardial ischemia.

Nicotine's effect on coronary vasomotor tone occurs primarily through noradrenergic stimulation of  $\alpha$  and  $\beta$  receptors associated with coronary vasoconstriction or vasodilation, respectively.<sup>9,10</sup> These competing influences on coronary blood flow appear to manifest differently based on whether patients are at rest or in a stressed state. A study by Czerin and colleagues demonstrated that in healthy patients with relatively short smoking histories and in a healthy nonsmoker control group, coronary blood flow increased by 25% and 40%, respectively, with nicotine use at rest.<sup>9</sup> However, when these patients were stressed with dipyridamole and while smoking during the examination, myocardial blood flow was reduced by 11% in the study group and 14% in the control group.<sup>9</sup> This is likely because the patients studied had relatively healthy coronary arteries that were able to maximally dilate when stressed. In this scenario, nicotine's dilatory effects are offset by nicotine's  $\alpha$ -receptor-mediated vasoconstriction effects.<sup>9</sup> Of note, patients in the study group experienced a somewhat diminished increase in coronary blood flow at rest with nicotine use, suggesting that even a short smoking history may damage the myocardial endothelium, rendering it less responsive to nicotine's vasodilatory effects.<sup>9</sup>

These principles similarly apply to

**TABLE 2** Nicotine Replacement Products<sup>28</sup>

Therapies	Doses	Half-life, h
Nicotine patch	If smoking > 10 cigarettes/d: start with 21 mg patch (wk 1-6), then 14 mg patch (wk 7-8), then 7 mg patch (wk 9-10) If smoking ≤ 10 cigarettes/d: start with 14 mg patch (wk 1-6), then 7 mg patch (wk 7-8)	4
Nicotine gum, lozenge	If 1st cigarette > 30 min upon waking: start with 2 mg If 1st cigarette ≤ 30 min upon waking: start with 4 mg Maximum: 24 gum pieces/d or 20 lozenge/d	2-3
Nicotine inhaler, nasal spray	Inhaler: 6-16 cartridges/d for up to 12 wk, then taper frequency of use over 6-12 wk Nasal spray: 1-2 doses/h, max of 5 doses/h or 40 doses/d for up to 3 mo	1-2

patients with underlying moderate-to-severe cardiovascular disease (CVD). With nicotine use at rest, patients with significant CAD do not experience as dramatic of an increase in coronary blood flow, which typically decreases or remains the same despite increased myocardial work.<sup>10</sup> This may be because patients with moderate-to-severe CAD often have flow-limiting stenoses and damaged endothelium that do not allow vessels to respond as efficiently to increased myocardial demand or to nicotine's  $\beta$ -receptor-mediated vasodilatory effects.<sup>10,11</sup> Moreover, when stressed, diseased coronary arteries are not able to further dilate and nicotine's  $\alpha$ -receptor-mediated vasoconstriction effects dominate.<sup>10,11</sup>

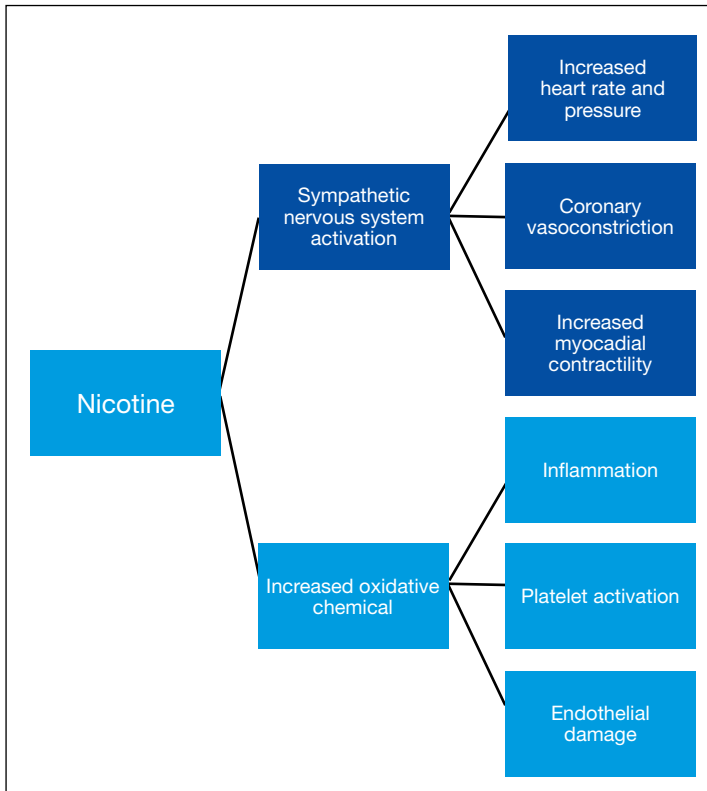
In a study by Quillen and colleagues of patients with moderate-to-severe CAD, the mean diameter of proximal coronary artery segments decreased by 5%, the distal coronary diameter decreased 8%, and the coronary vascular resistance increased by 21% while smoking at rest.<sup>12</sup> The investigators did not analyze how parameters changed when these diseased coronary arteries were stressed using a medication during MPI. However, it can be predicted that coronary arteries would have constricted to a similar or greater degree than observed in Czerin and colleagues' study, given that the underlying myocardium was diseased and more susceptible to nicotine's vasoconstriction effects.<sup>9</sup> Importantly, these studies have several limitations, most notably that they are older and have small sample sizes. Additionally, while statistically significant differences were found in the degree of changes in coronary circulation with nicotine use at rest and during stress, it is unclear whether this translates to a clinically significant and impactful finding.<sup>9-12</sup>

### Nicotine Replacement Therapy and Stress Testing

Given the association between cigarette smoking and CAD, medical practitioners strongly encourage patients to quit smoking to reduce their risk of adverse cardiovascular outcomes. Various smoking cessation treatments are available for patients. Common, readily accessible forms of therapy include nicotine replacement products (Table 2).

Early studies of NRT in patients with underlying CVD found an increased risk of cardiovascular events, such as myocardial infarction, presumably due to the nicotine content of these products.<sup>13,14</sup> However, the concentration of nicotine in NRT is substantially lower than that found in cigarettes and in some formulations, such as transdermal patches, nicotine is delivered over a prolonged period of time.<sup>15</sup> For this reason, NRT is thought to be safe in patients with underlying CVD and stable ischemic heart disease. A recent systematic review and meta-analysis found that while NRT may be associated with tachycardia, it did not increase the risk of more serious cardiovascular adverse effects (AEs).<sup>16,17</sup>

Given the lower nicotine concentration in NRT products, the associated hemodynamic effect of nicotine also is thought to be less pronounced. In a study conducted by Tzivoni and colleagues in patients with CAD using transdermal nicotine patches, no differences in blood pressure, heart rate, ischemia, or arrhythmias were found from baseline to 2 weeks.<sup>18</sup> These findings were further confirmed in a small study by Lucini and colleagues, which found that nicotine patches produced slight hemodynamic effects, but to a lesser extent than cigarette smoking.<sup>19</sup> For the NRT gum formulation, while a small

**FIGURE** Effect of Nicotine on Myocardium<sup>14</sup>

study found that 4 mg produced coronary vasoconstriction in patients with underlying CAD, a study by Nitenberg and Antony demonstrated that healthy and diseased coronary arteries did not significantly constrict while patients were using nicotine gum both before and after a cold pressor test, suggesting a lesser degree of coronary vasoconstriction than nicotine from cigarette smoking.<sup>20,21</sup> Similar findings have been described with the nicotine intranasal spray in a study by Keeley and colleagues, which showed no additional AEs on myocardial demand or vasoconstriction when an intranasal nicotine spray was added to cigarette smoking.<sup>22</sup> Importantly, a review of the transdermal and gum formulations found that these less pronounced hemodynamic effects were observed across different doses of NRT; however, further studies are needed to clarify the relationship between NRT dose and cardiovascular effects.<sup>23</sup>

Overall, NRT does not seem to activate the SNS to the same degree as nicotine obtained via cigarette smoking and likely does not increase the myocardial oxygen de-

mand as much. Additionally, by containing a lower concentration of nicotine, NRT may not impair the myocardium's ability to supply oxygen to coronary arteries to the same extent as nicotine from cigarette smoking. Therefore, the effects of NRT on MPI using a stress-inducing medication may not be as pronounced. However, due to study limitations, results should be interpreted cautiously.<sup>18-23</sup>

## CONCLUSIONS

Because of the close relationship between cigarette smoking and CAD, many patients with underlying CVD are either current smokers or may be using NRT for smoking cessation. Therefore, the question of whether to refrain from nicotine use prior to MPI is clinically relevant. Currently, there is a lack of high-quality studies demonstrating the effects of nicotine and NRT on coronary perfusion. Because of this, the impact of nicotine and NRT use on the accuracy of MPI using stress-inducing medications remains uncertain. Nevertheless, given that nicotine and NRT may largely affect the accuracy of imaging results, several institutions have adopted protocols that prohibit patients from using these drugs on the day of nuclear stress testing.

There are currently no data specifying the number of hours to hold nicotine products prior to cardiac stress testing. It is generally recommended that other medications that affect coronary blood flow be held for 5 half-lives before conducting MPI.<sup>4</sup> Following the same guidance for nicotine and NRT may present a reasonable approach to ensure accurate imaging results. Based on the discussed literature, patients should be instructed to refrain from cigarette smoking for at least 5 to 10 hours prior to MPI, given nicotine's half-life of about 1 to 2 hours.<sup>24</sup>

The data for NRT are less clear. While use of NRT may not be an absolute contraindication to conducting MPI, it is important to consider that this may affect the accuracy of results. Given this uncertainty, it is likely ideal to hold NRT prior to MPI, based on the specific formulation of NRT and that product's half-life. Further robust studies are needed to analyze the impact of nicotine and NRT on the accuracy of nuclear stress testing using a medication.

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The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

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## Ethics and consent

This study was deemed exempt from institutional review board approval.

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