# Arginase and Respiratory Viral Infections

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**Abstract:** Arginase activity in the lung has become a focus of research as modulation of this enzyme may result in desirable outcomes in a variety of pulmonary disorders. This review examines the current available literature for insights into how arginase modulation may alter the course of respiratory viral infection.

**Keywords:** Arginase, arginine, virus, lung, infection, nitric oxide.

## INTRODUCTION

Viruses are the most abundant and rapidly evolving pathogens that challenge the human immune system [2]. Further, respiratory viral infections are the most common type of human infection and result in a significant amount of morbidity and mortality around the world [3]. Clinically, infection may result in no symptoms, mild upper respiratory tract symptoms, pneumonia or, in the most severe instances, death.

The number of different viruses implicated in lung infections is numerous and includes rhinovirus, respiratory syncytial virus (RSV), adenovirus, influenza, parainfluenza, human metapneumovirus and coronavirus. However, in many cases a specific virus is not isolated. This may reflect a failure to isolate a known pathogen or may suggest the existence of an as yet unidentified pathogen(s).

The lung has developed effective defenses against infection as evidenced by the rarity of fatal lung infection. As part of this defense system, the lung produces nitric oxide (NO). There is a wealth of literature examining the importance of NO in the human lung in the context of viral infection [4]. Although where-ever possible this review will focus on arginase and the evidence linking arginase to the pathogenesis of viral lung disease, it is impossible to discuss arginase without referring to NO.

## NITRIC OXIDE:

The bulk of pulmonary NO is constitutively produced by lung epithelial inducible nitric oxide synthase (iNOS or NOS2) [5] through the oxidation of L-arginine to L-citrulline. There are 2 other isoforms of NOS which also metabolize L-arginine to L-citrulline but their contribution to NO production in the lung is less relevant. Alternatively, L-arginine can by hydrolyzed to form L-ornithine and urea by a class of enzymes known as arginases (Fig. **1**). There are 2 known arginases (I and II) and both can be found in the lung [6]. It should be noted that L-arginine can also be metabolised by a decarboxylase enzyme to produce L-agmatine or by an amidinotransferase enzyme as a first step to creatine production. The effect of these enzymes on L-arginine bioavailability in the lung will not be discussed further. (Though activity of arginine decarboxylase or arginine:glycine amidinotransferase has not been reported in the lung [1,7], arginine decarboxylase is present in macrophages [1]).

Most arginase related effects in viral lung disease are likely secondary to arginase effects on NO levels. Although in general, viruses do need some arginine to grow [8], there is no evidence that a human cell will deliberately create an arginine free environment to thwart a virus. At the other end of the spectrum, high amounts of arginine can also be toxic to viruses [9], however the toxic levels for a virus are approximately 1000 times that found in plasma (100uM) [6]. Levels this high would also be toxic to the cell itself.

Arginase can effectively reduce lung NO production by competing with NOS for L-arginine. Reduced bioavailability of NOS substrate leads to reduced enzyme activity and hence less NO production [10]. However, factors other than those that alter substrate availability may alter enzyme activity. Generally speaking most NOS regulation occurs transcriptionally [11]. Consistent with this, there is evidence that reduced L-arginine leads to phosphorylation of the eukaryotic initiation factor, eIF2$\alpha$. This in turn leads to inhibition of iNOS mRNA translation [12]. Thus there may be multiple mechanisms, in addition to enzyme-substrate availability, by which arginase may influence the production of NO, however the consistent paradigm is 'more arginase = less NO'.

## HOW DOES NO EFFECT VIRUSES?

It has been shown in a number of models that NO influences a broad range of viruses from large double stranded DNA viruses to smaller single stranded RNA viruses both *in vitro* [13-16] and in animal models [17-19]. Although this may suggest that NO affects viruses in a pleiotropic manner, *in vitro* studies point to a similar mechanism in most of these models; NO inhibits viral RNA replication [13-16, 20]. This may in part be related to nitration of specific viral proteins essential for RNA replication [21, 22].

NO may also modify host proteins. Indeed, NO can regulate a number of signaling molecules and transcription

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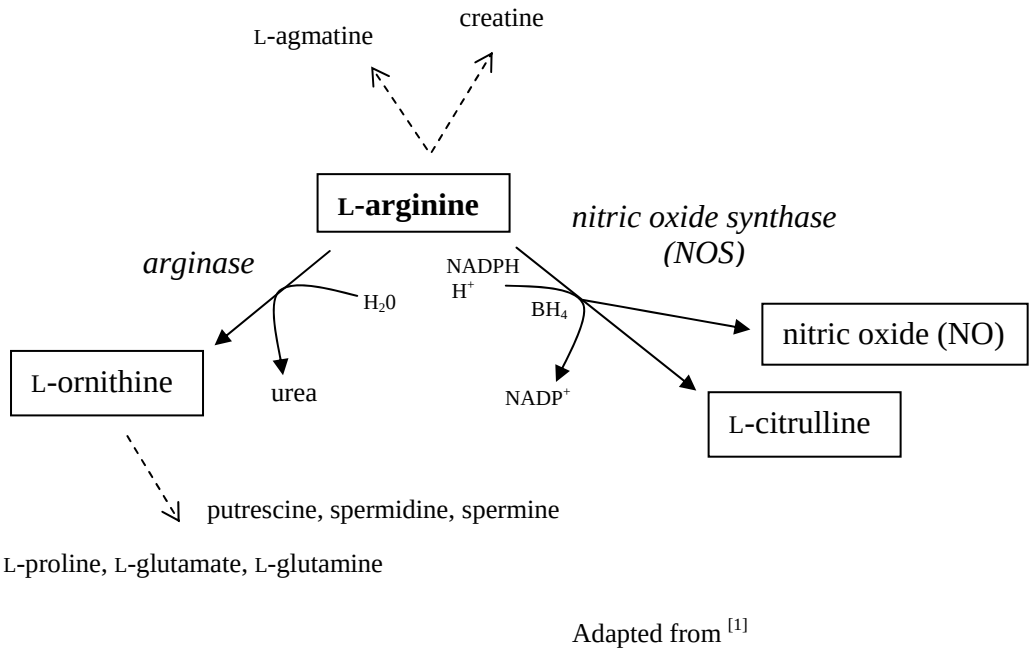


**Fig. (1).** Arginine metabolism.

factors in lung epithelial cells and thus have diverse effects in the lung [11]. NO effects in the lung include upregulation of ciliary motility [23], inhibition of sodium ion transport [24], altered mucous secretion [25], altered epithelial barrier function [26] , altered epithelial repair [27], altered cytokine production [28], modulation of airway tone [29] and pulmonary vascular tone [30].

In addition to these pulmonary effects, arginine levels or NO have also been linked to the function of multiple immune cells. Thus arginine deficiency impairs B cell maturation [31] , and decreases T cell proliferation and cytokine production [32]. In addition, innate immune cells such as macrophages [33], mast cells [34] and neutrophils [35] are all regulated to some degree by NO.

Thus, although NO may have specific effects on viral replication, this does not preclude multiple roles for NO. In fact, as described above, NO does modify numerous host proteins and processes. Thus the cumulative effect of NO may be beneficial or detrimental when examined in the context of viral infection *in vivo* [36, 37]. Further, depending on the model, contradictory findings may be seen. Thus in a mouse model of RSV infection, *NO production* increased airway hyperresponsiveness (AHR) and inflammation [19] however, in a guinea pig model using parainfluenza type 3 viral infection, the opposite was seen; *NO deficiency* was associated with increased AHR [38].

In general though, not enough NO allows viruses to avoid NO anti-viral effects and promotes infection, whereas too much NO leads to host pathology related to the production of nitrogen and oxygen free radicals. In addition to damaging the host, extra NO production may impact the virus in a potentially favorable way; NO can lead to an expanded viral quasispecies spectrum by enhancing viral mutation rates [39]. This may increase the chances of successful infection by improving virus adaptability and evolution. Titrating NO production will depend not only on substrate (arginine availability) but also enzyme (NOS, arginase) function. Whether a specific experimental model or infection will result in production of 'too much' or 'too little' NO and thus support a beneficial or harmful role for NO is difficult to predict. It is known that respiratory viral infections can result in enhanced production of NO or NOS in animal models [40-43] and humans [44]. However arginase activity is also altered by micro-organisms (see below) and arginine levels may also change for other reasons (nutrition, altered transport from outside to inside cell). These variables may account for some of the contradictory harmful and protective responses attributed to NO in the literature.

## VIRUSES AND ARGINASE:

Given the link between NO and viral infection one would expect that alterations in arginase would impact the pathophysiology of viral lung disease. Although there are both harmful and beneficial effects of NO, the bulk of evidence supports a protective role for NO in the setting of lung viral infection. Thus, increased arginase activity, which reduces NOS dependent NO production, would be expected to be associated with poor outcome.

There is some indirect evidence to support this hypothesis. There is a body of work that implicates arginase upregulation in Th2 cells, whereas Th1 cells upregulate iNOS [45]. Viral infections are cleared most effectively by a Th1 immune response. Thus, from a purely viral infection point of view, arginase downregulation (at least in host immune cells) would be desirable.

Although mycobacterium and toxoplasma species are not viruses, similar to viruses they are intracellular pathogens and require an effective Th1 response to be eradicated. These bacteria have evolved to induce a TLR mediated upregulation of arginase in macrophages allowing them to survive the harsh environment inside a phagocyte. In situations where arginase upregulation was eliminated, host survival was increased and lung bacterial load was decreased

[46]. *Helicobacter pylori*, another intracellular pathogen, has gone one step further and brings its own arginase enzyme with it. Mutant bacteria lacking this enzyme were efficiently killed by host cells as opposed to wild type bacteria which displayed enhanced resistance to killing [47]. Thus if intracellular pathogens *improve* their survival with increased arginase activity, arginase is likely not beneficial to the host in a viral infection. Similar strategies have not been described in viruses however, it is possible that viruses may trigger upregulation of host arginase in order to promote infection.

## ARGINASE DEFICIENCY:

Arginase 1 deficiency has been described in humans (OMIN 207800); arginase 2 deficiency has not been described. In these patients, as would be expected based on the hypothesis that less arginase is beneficial in viral infection, no mention of enhanced susceptibility to viral infection or immunodeficiency is made. There are multiple allelic variants of the arginase 1 gene described in humans but none are associated with a gain of function. However, there is a description of NOS2 allelic variants associated with increased NO production and resistance to malaria [48]. Interestingly, the malaria parasite, *Plasmodium falciparum*, like *H. pylori*, brings its own arginase when it infects cells [49].

Arginase inhibition in the setting of viral infection in humans has not been described. Arginine deiminase (hydrolyzes arginine to citruline) has been studied in specific cancers [50] as a mechanism of reducing arginine related angiogenesis. Interestingly there is an ongoing clinical trial and a patent (WO/2004/046309) registered with the World Intellectual Property Organization to study this enzyme in humans in the setting of influenza infection [51]. This reinforces the complexity of nitric oxide biology in the setting of viral infection. It may be possible that increased arginase increases the likelihood of viral infection (by reducing arginine related NO production and host defense) however, once infected reduced arginine may improve outcomes (by limiting NO related free radical production).

There are 3 arginase knockout mouse models. Arginase 1-/- mice die by 2 weeks of age. Arginase 2-/- mice display no obvious pathology and arginase 1/2 double knockout mice also die by 2 weeks of age [52]. Based on the current literature, it might be hypothesized that arginase 2 deficient mice have increased susceptibility to viral infection, however, this remains to be confirmed.

In addition to arginase and NOS, a third enzyme that controls arginine levels intracellularly is the cationic amino acid transporter (CAT). This membrane protein imports arginine into the cell. There are no deficiencies described in humans. Of note, a murine cationic amino acid transporter also acts as a cell receptor for a murine retrovirus [53]. Human CAT may also have a similar role in humans but this has not been described.

CAT2 deficient mice are more susceptible to the intracellular pathogen *Toxoplamsa gondii* [54]. Viral infections have not been studied in this mouse model.

## ARGININE SUPPLEMENTATION:

If more arginase activity is hypothesized to result in reduced arginine and hence reduced NO production and a worse outcome, increasing arginine bioavailability should improve outcomes in lung viral infections. In humans, zinc/arginine supplementation did not alter antibody titres to influenza post vaccination in elderly patients [55]. Incidence of infection was not examined. In a murine model, arginine supplementation did improve mitogen induced splenocyte proliferation however, outcome of influenza infection (weight loss) was not different between 'regular' diet and arginine supplemented mice [56]. However, it has been argued that arginine supplementation is associated with a beneficial effect in the right setting. Thus, moderately ill patients will benefit the most; mildly ill patients generally will get better regardless of intervention and very sick patients require more than simple nutritional interventions [57]. Currently, there is no consensus to arginine supplementation in either acutely unwell or stable patients. Given the potential risks (vasodilatation, fibrosis), further study is required before this becomes routine practice [58-60].

## SUMMARY:

Nitric oxide is a key molecule in the immune defense of the lung. Although the bulk of evidence supports an antiviral role for NO, given the multiple ways NO influences molecules, cells and the lung, in the setting of lung infection both beneficial and harmful effects have been reported. Increased arginase activity reduces nitric oxide synthase dependent NO production and thus may be harmful in the setting of viral infection. Conversely, arginine supplementation or arginase inhibition may be beneficial. However, more study is needed before either of these hypotheses can be accepted.

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## ABBREVIATIONS

| | | |
|---|---|---|
| NOS | = | Nitric Oxide Sythase |
| Arg | = | Arginase |
| AHR | = | Airway hyper-reactivity |
| RSV | = | Respiratory Syncytial Virus |
| CAT | = | Cationic Amino Acid Transporter |

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