POLYMORPHISMS OF MATRIX METALLOPROTEINASES (MMP) IN COPD

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ABSTRACT

COPD is a chronic disease of the lung that is characterized by decreased air flow and is associated with abnormal chronic inflammation in the airways and development of extensive tissue remodeling. Matrix metalloproteinases (MMP) comprise a family of proteolytic enzymes capable to degrade practically all components of extracellular matrix (ECM) and they play a key role in normal physiological processes of development, tissue remodeling and repair, as well as in various pathological conditions. Based on their substrate specificity and structural organization they are subgrouped into collagenases, stromelysins, gelatinases, matrilysins, and membrane-type matrix metalloproteinases.

The MMP activity is very strictly controlled at the level of gene transcription, latent zymogene activation, and inhibition by endogenous inhibitors. Most of MMP genes are highly polymorphic with allele-specific effects on transcriptional activity of the corresponding gene or on the enzyme activity.

In the current report we attempt to summarize the information about the role of polymorphisms of MMPs in development and progression of COPD. In addition we comment our own data concerning the effect of two promoter polymorphisms: MMP1 - 1607insG (1G>2G, rs1799750) and MMP3 - 1171insA (5A>6A, rs3025058) on the risk of COPD, which suggest that SNPs do not represent risk factors for development of COPD, but may affect the lung function.

Keywords: COPD, MMP, polymorphisms, risk factors

Introduction

COPD is a chronic disease of the lung that is characterized by decreased air flow and it is associated with abnormal chronic inflammation in the airways and development of extensive tissue remodeling. One of the most prevailing hypotheses for pathogenesis of COPD proposes that the inhaled irritants of cigarette smoke or air pollution lead to recruitment and stimulation of neutrophils and macrophages, which patrol the lower airspaces under normal conditions. These activated inflammatory cells produce and release reactive oxygen species (ROS) and variety of proteolytic enzymes, which degrade the extracellular matrix (more specifically elastin), remodel the lung tissue and lead to emphysema. The latter one is one of the features of COPD (7, 12, 29, 37, 43).

The decomposition of the components of basement membrane and ECM is provided by several groups of proteolytic enzymes including plasminogen activators (PAs), cathepsins, matrix metalloproteinases (MMPs), adamalysins (ADAMs, a disintegrin and metalloproteinases) and ADAMTSs (a disintegrin and metalloproteinase with thrombospondin motifs) (1, 8, 23, 40, 51).

Matrix metalloproteinases (MMP) comprise a large family of zinc-proteolytic enzymes that cleave various components of the ECM and BM. They present the family of MMPs consists of more than 20 members (currently 24 in humans), which differ in substrate specificity, regulation and potential interactions with additional MMPs and TIMP family members (9, 33, 47, 50, 68).

Structurally most of the MMPs share five common domains: a hydrophobic signal peptide at the N-terminal end; a propeptide with a conserved cysteine residue into “cysteine switch” motif; the catalytic domain containing a highly conserved zinc binding sequence; a proline-rich linker peptide, called “hinge region”; and a C-terminal hemopexin domain (Fig. 1A). The MMPs with the common 5-domain structure belong to the subgroup of simple hemopexin-domain-containing MMPs (MMP-1, MMP-3, MMP-8, MMP-10, MMP-12, MMP-13, MMP-19, MMP-20, MMP-27). There are exceptions from this structural similarity: matrilysins (MMP-7 and MMP-26) and MMP-23 do not contain the linker peptide and the hemopexin domain; the gelatinases (MMP-2 and -9) contain in their catalytic domain three fibronectin type II inserts that are important for collagen binding; and MMP-9 has an extra collagen V-like sequence within the catalytic domain downstream of the Zn²⁺ binding; a furin cleavage site (a recognition motif for furin-like enzymes in MMP-11, 28, 21, 23 and all membrane-type MMPs) (Fig. 1B); and a transmembrane domain accompanied by a short cytoplasmic domain anchoring present in the membrane-type MMPs (MMP-14, -15, -16 and -24) (Fig. 1C). Instead of the transmembrane and
cytoplasmic domains there is a glycosylphosphatidylinositol (GPI)-anchoring domain in MMP-17 and MMP-25 (10, 19, 33, 47, 48, 50, 68, 69).

MMPs are naturally inhibited by specific inhibitors called tissue inhibitors of metalloproteinases, TIMPs (33, 47, 48, 68), but they can also be inhibited by metal chelators. MMPs are secreted as pro-enzymes (zymogens) which require extracellular activation and act in physiological pH (33, 47, 48, 68).

The cleavage of the “cysteine switch” containing propeptide activates the latent zymogens. MMP proenzymes may be activated by variety of enzymes such as trypsine 2, cathepsines G, B and L, neutrophil elastase, plasminogen activators etc. Activated MMPs have capability for auto-activation and activation of other proMMPs (33, 69). Important roles in activation of secreted proMMPs have the MT-MMPs and TIMPs (particularly TIMP-2) (2, 28, 33, 69). Some of the proMMPs containing furin cleavage site are activated intracellularly by furin (69).

On the basis of substrate specificity of MMPs they can be classified into five groups: collagenases (MMP-1, -8 and -13), stromelysins (MMP-3, -10 and -11), gelatinases (MMP-2 and -9), matrilysins (MMP-7 and -26), and membrane-type matrix metalloproteinases (MT-MMPs) (47, 69). MMPs can act not only as proteinases, but also as molecules involved in cell-cell and cell-matrix signalling (9, 65). Overexpression or down-regulation of MMPs has been associated with several pathological conditions, including rheumatoid arthritis, osteoarthritis, cardiovascular diseases, periodontitis, dermal photoaging, chronic ulcerations, gingival overgrowth and different types of cancer (2, 3, 4, 5, 17, 18, 36, 39, 49, 63).

### Implication of MMPs in COPD

Since the extracellular matrix of the lung is predominantly composed of elastin and to a lesser amount collagen and since emphysema is characterized by the destruction of alveolar walls abstraction occurs due to destruction of elastic parenchymal tissue surrounding the small airways, the research interest has been focused initially on the enzymes with elastolytic activity, such as neutrophil elastase (NE), MMP-12, MMP-2, MMP-9. Further, collagenases have also been involved in the studies and found to be important in emphysema and COPD.

There is considerable evidence from studies with animal models and patients with COPD that several MMPs, particularly MMP-1 (collagenase 1), MMP-2 (gelatinase A), MMP-9 (gelatinase B) and MMP-12 (macrophage metalloelastase), are important in airway inflammation and the development of emphysema in COPD. It has been reported that transgenic mice overexpressing human MMP-1 develop lung changes like disruption of the alveolar walls and coalescence of the alveolar spaces, which are similar to the morphological changes observed in human emphysema (14). In another study with MMP-12 knockout mice it was demonstrated that MMP12 (-/-) mice did not have increased numbers of macrophages in their lungs and did not develop emphysema in response to long-term exposure to cigarette smoke (27). Several studies with patients with COPD and emphysema have reported that MMP-1, MMP-2, MMP-8 (collagenase 2), MMP-9, MMP-12 and MT1-MMP (MMP-14) protein and mRNA levels are increased in lung tissue, BAL and induced sputum of the patients than in controls, although there were also some controversial findings (13, 16, 23, 30, 41, 46, 53, 55, 61).

![Fig. 1. General structure of MMPs](image)

Adapted according to Egeblad M. and Werb Z. (19)
The high protein level of MMP-1, detected by immunohistochemistry was localized to the Type II pneumocytes in patients with emphysema, but not in normal control subjects or smokers without emphysema (30). However, no difference in MMP-12 expression level was found in the lung parenchyma of patients with emphysema compared with controls. On opposite, highly elevated MMP-12 levels were reported for the induced sputum from patients with COPD compared to healthy smokers and non-smokers (16). Moreover, increased levels of MMP-12 have been found earlier in BAL fluid, cultured alveolar macrophages and tissue sections from patients with COPD in comparison to healthy controls (45).

Similarly, increased levels of total and active MMP-8 and MMP-9 were found in the induced sputum of COPD patients compared with the controls (67). Moreover, zymography analyses have revealed a moderate and intense increase of proMMP-2 and proMMP-9, respectively in BAL fluid of patients with COPD. The increase enzyme activity was accompanied by markedly increased expression of MMP-9 (gelatinase B) and MMP-8 (collagenase-2) by neutrophils and of MMP-2 (gelatinase A) and MMP-1 (collagenase 1), but not MMP-13 (collagenase 3), by alveolar and interstitial macrophages and in epithelial cells (61). In addition it has been observed that upon a stimulation with lipopolysaccharide (LPS), interleukin (IL)-1 beta, or cigarette smoke-stimulation with lipopolysaccharide (LPS), extracellular stimulus induce signal transduction pathways leading to activation of transcriptional factors as NF-kB (nuclear factor kappa B), STATs (signal transducers and activators of transcription), Smad family, ETS transcriptional factors, AP-1 (activation protein-1) complex of transcriptional factors, etc. (2, 20). The latter one is a converging point for ERK1,2, JNK and p38 MAP kinase pathways (2).

In this respect the naturally occurring DNA sequence changes in the regulatory regions, particularly the promoters of the genes encoding MMPs were supposed to affect the transcriptional activity and thus to influence the balance between MMPs and TIMPs and be involved in development and progression of COPD. Now there is strong evidence that the expression levels of several of the MMPs are affected by polymorphisms in the promoter regions of the genes encoding those enzymes (73).

MMP-1 (interstitial collagenase-1)
The interstitial collagenase-1 (MMP-1) is one of the principal proteinases capable of cleaving triple helical fibrillar collagen of type I, II, III and V into fragments, which denature into gelatin and are further degraded by other MMPs, such as gelatinases (68). Particularly, MMP-1 has a preference to type III collagen. The gene of MMP-1 is located at 11q22-q23 locus and several SNPs and insertion/deletion polymorphisms have been identified mainly in regulatory regions (promoter, 3'UTR, 5'UTR and introns) (24, 56). At least 20 polymorphisms (3 in the promoter, 4 in 3'UTR, 1 in 5'UTR, 11 in introns, and one exonic SNP) have been studied in relation to COPD as a great attention has attracted the SNP at -1607 of MMP1 (-1607insG, rs1799750) (56). The insertion of a second G nucleotide at position -1607 of MMP1 (-1607insG, rs1799750) generates a new 5'-GGA'3' sequence that corresponds to a recognition sequence for members of Ets family of transcriptional factors (22, 56). The functional analyses have proven that the 2G (insG) allele and homozygosity results in increased transcriptional activity in different cell types compared to 1G (G) allele and homozygotes (21, 56, 72, 80). The case-controls studies in different ethnic and race population have revealed no difference of the genotype and allele frequencies between patients with COPD and control groups.

Polymorphisms in MMP Genes and COPD
The expression level and activity of MMPs are normally tightly controlled in several ways including transcriptional regulation, activation of latent zymogens and inhibition of MMP activity by the endogenous tissue inhibitors of MMPs, TIMPs.

It appeared, however, that for most MMPs, the key step is the transcriptional regulation (18, 20). An exception is MMP-2 that is wildly expressed in relatively high levels in majority of cell types even in quiescent state (73). Most members of MMP gene family share a common cis-elements in their promoters, which allows coordinative regulation by variety of extracellular factors, such as cytokines (IL-1β, IL-1α, TNF-α, TGF-β), growth factors (bFGF, EGF, VEGF), bacterial LPS, oxidative stress factors, xenobiotics (20, 31, 33). The extracellular stimulus induce signal transduction pathways leading to activation of transcriptional factors as NF-kB (nuclear factor kappa B), STATs (signal transducers and activators of transcription), Smad family, ETS transcriptional factors, AP-1 (activation protein-1) complex of transcriptional factors, etc. (2, 20). The latter one is a converging point for ERK1,2, JNK and p38 MAP kinase pathways (2).
(11, 24, 38, 42, 64, 66, 78). Paradoxically, however the MMP1 -1607 G allele (1G allele) was reported to associate with a fast rate of decline in lung function especially in a haplotype with MMP12 Asn357 (34).

Recently we conducted a case-control study recruited 163 patients with COPD and 172 control non-affected by lung diseases individuals and genotype them for MMP1 -1607insG by PCR-RFLP method (70). The observed genotype and allele frequencies of patient and control groups did not differ significantly, however the COPD patients homozygous for the high-producing 2G allele (2G/2G) of MMP1 had slightly higher, although not statistically significant, risk for COPD in comparison to those with genotypes supposed to determine lower promoter activity of MMP1 gene. In addition carriers of 2G/2G MMP1 genotype had lower values of the spirometric index FEV1% pr. compared to the patients with other genotypes, as this difference was more distinct, reaching a statistical significance, in the subset of patients with smoking history. Thus, our results suggested that alteration in MMP1 gene expression caused by MMP1 -1607insG polymorphism may be involved together with other factors in the decline of lung function of smokers with COPD.

Fig. 2. Cell types producing matrix metalloproteinases (MMPs) and tissue type of inhibitors of metalloproteinases (TIMPs) and possible role of matrix MMPs and MMP/TIPM imbalance in development of tissue remodelling and emphysema in COPD
IL-8 - interleukine 8; LTB4 - leukotriene B4; MCP-1 - monocyte chemotactic protein 1; MIP-1α - macrophage inflammatory protein-1alpha; NE- neutrophil elastase, ROS - reactive oxygen species; MMP-1 - collagenase 1; MMP-2 - gelatinase A; MMP-3 - stromelysin-1; MMP-8 - collagenase 2; MMP-9 - gelatinase B; MMP-12 - macrophage metalloelastase; MT1-MMP - membrane type 1 MMP (MMP14). Adapted according to data presented in references 6, 15, 40
MMP-3 (stromelysin-1)
Stromelysin-1 (MMP-3) is one of the closely related to collagenases enzymes with respect to structure and substrate specificity. It is able to cleave the net-work-forming collagens (type IV, VII and X) and in less extend the fibrillar collagens (type III, V and XI), having preference to the type IV collagen that form the basal membrane (21, 69). MMP-3 is shown to possess elastolytic activity (69) and it is believed to play important role in matrix remodeling, including in the lung. In addition, MMP-3 is also involved in activation of some other members of the MMP family, including MMP-1 (26).

The gene of MMP-3 is located 11q23 in close proximity to MMP1. In MMP3 an insertion/deletion of an A nucleotide at position -1171 in promoter region of MMP3 has been identified. This promoter polymorphism (5A/6A, -1171insA, rs3025058) results in transcriptional activity of the 5A homozygous in approximately double than the 6A homozygous (73, 74). DNA-protein interaction assays have showed the binding of two putative transcriptional factors to the region of MMP3 gene promoter. One of the nucleoprotein factors bound preferentially to the 6A allele (the allele associated with lower promoter strength), whereas the other interacted similarly with both alleles. These data suggest that the putative transcriptional factor, binding with higher affinity 6A allele it likely a transcriptional repressor (73, 74).

The studies concerning MMP3 -1171insA in COPD are very limited in number. This polymorphism is reported to be no risk factor for the development of COPD in populations from Brazil (60), Taiwan (11) and Italy (59), while 6A/6A genotype and 6A allele were significantly associated with more severe disease and ling functional decline over time (59).

Our results obtained from a recent case-control study with 162 patients with COPD and 172 controls genotyped for MMP3 -1171insA with PCR-RFLP method showed no difference in the genotype and allele distribution between COPD patients and controls (70). Thus, our data are in accordance with those aforementioned ones and suggest that the -1171insA promoter polymorphism in MMP3 may not represent a predisposing factor for development of COPD.

MMP-2 (gelatinase A) and MMP-9 (gelatinase B)
Gelatinases (MMP-2 and -9) digest type IV collagen, which is an important component of basement membrane. Both enzymes can also degrade elastin (69) and the high expression of these enzymes in lung tissue, BAL fluid and induced sputum of patients with COPD and emphysema was supposed to be implicated in elastolytic degradation and remodeling of airways (61, 67) MMP-2 is regularly expressed by most of the cells, whereas MMP-9 expression is induced by several factors (12-O-tetradecanoylphorbol-13-acetate [TPA], growth factor, cytokines and so forth) (58, 68).

The MMP2 is mapped to 16q13 and MMP9 to 20q11.2-q13.1 in a locus close to those of MMP24 (MT5-MMP) (69). In the case of MMP2 three functional polymorphisms have been identified in the promoter of the gene. Two of them are transitions of C to T at positions -1306 and -735 (MMP2 -1306C>T, rs243865 and MMP2 -735C>T, rs2285053) and the third SNP is a transition of G with A at position -1575 (MMP2 -1575G>A). The previous two SNPs are in linkage disequilibrium as the T alleles of both SNPs and the -1306T -735T haplotype result in disruption of a Sp1 regulatory element and striking decreased promoter activity in macrophages and epithelial cells. The -1306T -735T haplotype displays an even lower promoter activity and mRNA expression compared with the haplotype consisting of only one T allele at the -1306 or -735 site, indicating an interactive effect of these two SNPs on MMP2 transcriptional function (20, 54, 75, 79). The third SNP, MMP2 -1575G>A, is located immediately 5’ to an estrogen receptor (ER) binding site and the –1575G allele functions as an enhancer, whereas the –1575A allele disrupts the ER binding and results in significantly decreased transcriptional activity (25). The MMP2 -1306C>T and MMP2 -1575G>A are also in linkage disequilibrium and the linked variants –1575A_–1306T versus the wild type –1575G_–1306C haplotype demonstrated an additive reduction in estrogen-dependent reporter activity (25).

The associative studies of MMP2 -1306C>T with COPD have created negative results concerning the effect of this polymorphism on susceptibility to COPD (64, 66), however the carriers of MMP2 -1306TT genotype appeared to have excess FEV1 decline and a lower mean of FEV1% pr. at the last survey compared to wild type carriers (66).

Several polymorphisms in MMP9 gene have been reported as three of them (two in the promoter region and one in a coding sequence) are found to be functionally important (24, 73, 76, 77). The C to T transition at position -1562 (MMP9 -1562C>T, rs3918242) was found to result in higher transcriptional rates for the T allele than C allele promoter (77). The second functional promoter polymorphism is a microsatellite polymorphism of variable number of CA repeats from 14 to 25 at position -131 bp, (previously -90 bp) (MMP9 -90(CA) (14-24), rs2234681), which is localized immediately adjacent to the proximal AP-1 binding site. This polymorphism was suggested to affect promoter activity and create a sequence-specific DNA binding protein site. Variation in the length of this repetitive element was shown to modulate...
promoter activity in an in vitro reporter assay, with the highest promoter activity being observed in constructs bearing the longest [(CA)₃] element (52). Similarly, esophageal carcinoma cell lines with low MMP-9 enzymatic activity were shown to have the number of d(CA) repeats shortened from 21 to 14 or 18, whereas those cell lines with high MMP-9 activities - 21 or 23 d(CA) repeats (62).

The third functional polymorphism in MMP9 is a transition of T to G in exon 6 and results in a substitution of glutamine to arginine at codon 279 (MMP9 Glu279Arg, Q279R, rs17576) (76). The Q279R polymorphism in exon 6 is located in the catalytic domain of the MMP-9 enzyme and within one of the fibronectin type-II like repeats required for binding of the enzyme to its substrate elastin. The substitution of the uncharged amino acid (glutamine) by a positively charged amino acid (arginine) has been supposed to alter protein confirmation, leading to a change in substrate-binding and enzyme activity (76).

A number of studies have been conducted to provide evidence for the role of sequence variations in MMP9 with emphysema and COPD (11, 24, 34, 38, 42, 44, 60, 66, 67). Most frequently MMP9 -1562C>T polymorphism has been analyzed and generally no effect of this SNP has been found on susceptibility of COPD (24, 38, 60, 64). However, in a study with COPD patients from Taiwan, the MMP9 -1562TT genotype, and especially carriers of double homozygous CYP*2A/*2A_MMP9 1562TT genotype had significantly higher (2.4-fold and 3.3-fold, respectively) risk of COPD (11). Moreover, the less common T allele has been reported to be associated with severity of COPD disease progression in patients from Bashkortostan Republic (38). An opposite result was reported for a Korean population: the frequency of the variant T allele was significantly lower in the cases than in the controls suggesting that individuals with at least 1 variant T allele were at a significantly decreased risk of COPD when compared with those with homozygous wild-type alleles (42). In case of MMP9 Glu279Arg SNP the 279Arg and the haplotype comprising the 279Arg and the CA long allele of CA promoter polymorphism were also found in non-Hispanic white and Hispanic populations from New Mexico to represent risk factors for COPD (64).

**MMP-12** (macrophage metalloelastase)

MMP-12 has attracted much attention because of its elastolytic activity and presence in high level in the induced sputum, BAL fluid cultured alveolar macrophages, and tissue sections of patients with COPD compared to healthy controls, including smokers and non-smokers (16, 45). The gene of MMP-12 is located in the 11q22 region, where the genes of eight MMPs are mapped: MMP7-MMP20-MMP8-MMP10-MMP1-MMP3-MMP12-MMP-13 (GeneBank). So far, mainly two of the sequence variances described in MMP12 have been studied in association with COPD and emphysema: the promoter polymorphism -82A>G (rs2276109) and the SNP in a coding region leading to substitution of 357 asparagine with serine (Asn357Ser, N357S, rs652438) (24, 34, 38, 42, 60, 66, 78).

The substitution of A to G at position -82 is located in region adjacent to the cis-element AP-1 binding site and it was shown that the polymorphism influences the binding of the transcription factor AP-1: a higher binding affinity of AP-1 to the A allele was associated with higher MMP-12 promoter activity in vitro in transient transfection studies in U937 and murine lung macrophage cells (35). The functional effect of the MMP12 Asn357Ser SNP has not been proven yet, but the change of amide amino acid asparagine to the hydroxylic serine has been suggested to alter the catalytic activity of the protein (34). Most of the aforementioned case-controls studies have found that none of studied MMP12 polymorphisms are predisposing factors for COPD (38, 42, 60, 66). However, in a large study involving COPD and controls from six European centres the common A allele of MMP12 -82A>G SNP was associated with increased risk of COPD in general and both in severe/very severe and mild GOLD stage of disease (24). Moreover, the A allele of -82A>G, as well as the common A_A (A_Asn) haplotype of MMP12 -82A>G and Asn357Ser SNPs were found to represent a greater risk of developing severe/very severe disease and the A-A haplotype was also associated with significantly lower predicted FEV1 (24). In another study concerning a Chinese population, carriers of homozygous MMP12 357Asn genotype and having concomitantly MMP9 -1562C>T heterozygous and MMP12 357Asn homozygous genotypes were reported to be of higher risk for development of smoking-induced COPD (78).

**MMP-8 (collagenase-2) and MMP-14 (MT1-MMP)**

MMP-14 is one of the membrane type MMPs, which has been shown to involved in activation of proMMP-2 on the cell surface in the presence of a low concentration of TIMP2 (32). Two SNPs in the promoter region (-165G>T and -72G>A) and five in exons (+221C>T in exon 1, +6727C>G and +6767G>A in exon 5, +7096T>C in exon 6, and +8153G>A in exon 8) have been studied in association with COPD. No difference in genotype frequencies of these polymorphisms were found between the COPD patients and the controls either in Japanese and Egyptian ethnic groups (57). However, due to the observed higher frequency in the Egyptian COPD group than the control group of the haplotype -165T/+221T/+6727C/+7096C, it
was suggested that this haplotype might be involved in the pathogenesis of COPD (57).

MMP-8 or neutrophil collagenase has been found to have similar efficiency to MMP-1 in cleaving collage and is produced at increased levels in conditions with prominent inflammation, including COPD (61, 67). For the MMP8 gene (11q22.3) three functional SNPs have been identified: MMP8 -799C>T, -381A>G and +17C>G (71). It was reported that the minor alleles +17G and -381G were in complete linkage disequilibrium and A promoter fragment containing the three minor alleles (-799T, -381G and +17G) had 3-fold greater activity in chorion-like trophoblast cells compared with the promoter construct containing the major alleles (71).

Although MMP-8 has been thought to play an important role in the development of COPD so far there is no study aiming to evaluate the involvement of the described functional MMP8 polymorphism as risk factors for COPD or disease severity. So, the role of MMP8 polymorphisms in COPD remains to be clarified.

Conclusions
COPD is a complex multifactorial disease characterized with abnormal chronic inflammation in the airways and development of extensive tissue remodeling. The latter process is considered to be a result of impaired balance of proteases and antiproteases, as matrix metalloproteinases (MMP) and their intrinsic inhibitors (TIMPs) play a pivotal role. There is strong evidence that MMP-1, MMP-2, MMP-8, MMP-9, MMP-12 and MT1-MMP (MMP-14) are important in airway inflammation and the development of emphysema in COPD. Since the level of expression and enzyme activities of MMPs are very strictly controlled at the level of gene transcription, latent zymogene activation, and the development of emphysema in COPD.

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