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# Lung Scintigraphy in COPD

Jann Mortensen, MD, DMSc,[*,†,‡] and Ronan M.G. Berg, MD, PhD[*,§]

**Ventilation-perfusion scintigraphy is a functional imaging biomarker that has the potential of captivating the heterogeneity of chronic obstructive pulmonary disease (COPD). It specifically images the distribution of ventilation and perfusion within the lungs, which is a critical pathophysiological component of COPD. The extent of ventilation defects and ventilation inhomogeneity, as well as the ventilation-perfusion ratio distribution thus correlate with severity of disease. Furthermore, specific scintigraphic patterns, such as the "stripe sign" may detect centrilobular emphysematous lesions with a higher sensitivity than other imaging techniques. Although ventilation-perfusion scintigraphy may conceivably detect COPD before any specific changes can be detected by spirometry or high-resolution CT, it is currently mostly used in the workup of lung volume reduction treatment, and for diagnosing various complications and comorbidities of COPD when combined with low-dose CT.**


## Introduction

Chronic obstructive pulmonary disease (COPD) is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contribution of which varies from person to person.[1] The diagnosis is based on relevant symptoms, particle/gas exposure (most often tobacco smoke), and spirometric findings of airflow limitation that is not fully reversible.[1] COPD is classified as GOLD 1-4 according to the reduction in ventilatory capacity, as evaluated spirometrically by the forced expiratory volume in 1 second ($FEV_1$). Unfortunately, $FEV_1$ and other spirometric indices are largely inadequate for describing the heterogeneity of COPD. First, spirometric indices are typically not affected during the very early stages of disease, and second, they only vaguely reflect the severity of symptoms, quality of life, and exercise performance during more severe COPD.[2] Although there is currently a focus on additional measures which may better explain the variation in individual disease burden in COPD patients,[2] clear alternatives have not yet emerged. In the present review, ventilation-perfusion (V/Q) scintigraphy is highlighted as a promising functional imaging biomarker for phenotyping COPD, detecting early COPD, and for evaluating specific treatment responses.

## Pathophysiology of COPD

COPD involves the destruction of alveolar septa and respiratory bronchioles and inflammation with the invasion of various immune cells, notably neutrocytes, into the bronchial walls and lumen.[3,4] While the former leads to a loss of parenchymal elastic recoil, and thus hyperinflation and peripheral airway obstruction, inflammation causes obstruction of both large and small airways, both due to excess mucus within the airways as well as by triggering bronchoconstriction.[4,5] Furthermore, neutrocyte degranulation products, such as elastases, contribute to the loss of pulmonary elastic recoil.[5] Accordingly, neutrophilic inflammation in the lungs as visualized by $^{18}$F-FDG PET/CT has been found to be greatest in lung regions with emphysema predominance, and to correlate with clinical measures of disease severity in the patients with stable COPD.[6]

The abovementioned changes render the distribution of ventilation more inhomogeneous, as observed during all grades of COPD. The degree is mild in the early stages of disease where inflammation and tissue destruction are

*Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark.
†Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.
‡Department of Medicine, The National Hospital, Torshavn, Faroe Islands.
§Faculty of Life Sciences and Education, University of South Wales, Pontypridd, United Kingdom.
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Address reprint requests to Jann Mortensen, MD, DMSc, Department for Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, University Hospital of Copenhagen, Juliane Maries vej 8; DK-2100, Copenhagen Est, Denmark. E-mail: Jann.mortensen@regionh.dk


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principally present in peripheral lung zones, while more severe inhomogeneity is evident in later and higher COPD stages, where the more central bronchioles and bronchi are also involved. Indeed, the initial changes probably take place in the small airways, as smoking even in the absence of clinical COPD leads to a notable inhomogeneous distribution of albumin radioaerosol deposition in the lungs,[7] which is characteristic of low flow rates in the small airways.[8]

Although hypoxic vasoconstriction ensues in less ventilated regions during all stages of COPD, the distribution of ventilation and perfusion throughout the lungs becomes unequal, thus impairing pulmonary gas exchange.[9] Changes in pulmonary vascular function triggered by the direct effects of particle/gas irritants or the associated inflammatory pathways contribute to this, and appear to predominate during lower COPD-stages, and furthermore may precede any detectable changes in ventilation in patients prone to develop COPD.[10,11]

High-resolution CT (HRCT) is the method of choice for visualizing and quantifying emphysema, and classifying it morphologically into centrilobar, panlobular, paraseptal, and irregular airspace enlargement subtypes.[12] However, given the pertinence of the distribution of ventilation and perfusion to the pathophysiology of COPD, V/Q scintigraphy may unveil several aspects of disease that are not detected by HRCT which will be outlined below.

## Ventilation and Perfusion Scintigraphic Findings in COPD

Both ventilation and perfusion inhomogeneity can be assessed separately or combined by planar or tomographic (SPECT) V/Q scintigraphy (Fig. 1).[13] While perfusion scintigraphy is performed with [$^{99m}$Tc] macroaggregated albumin, micron-sized, and submicron-sized aerosols ($^{99m}$Tc-labeled DTPA and $^{99m}$Tc-labeled clusters of carbon particles [Technegas], respectively) or inert radioactive gases ($^{133}$Xe and $^{81m}$Kr) may be used for ventilation scintigraphy. The quality and information gained from ventilation scintigraphy depends critically on the tracer. Hence aerosol tracers tend to deposit and create "hot spots" in the central airways when airway resistance is increased. This is more pronounced for the micron-sized DTPA aerosol than for Technegas, as the latter may be considered a "pseudogas,"[14] but in severe emphysema ventilation scans that are representative of the actual physiological distribution of ventilation are nonetheless best achieved by the use of inert gas tracers.[15] In head-to-head comparisons in severe COPD, $^{81m}$Kr thus penetrates further into the peripheral airways than Technegas while "hot spots" are also avoided (Fig. 2).[15]

The results and interpretation of a ventilation scan in the COPD patient depend not only on the tracer of choice, but also on the imaging technique. Hence, the severity and extent of ventilation defects are detected more accurately by SPECT (Fig. 2), and furthermore correlate more closely with signs of airway obstruction, hyperinflation, and emphysema as evaluated by lung function testing than when based on planar imaging.[16,17] Formalized SPECT-based assessments of COPD-associated ventilatory disturbances have furthermore been reported to correlate with severity of patient-reported symptoms and the extent of emphysema evaluated by HRCT.[18,19] Indeed, the extent of ventilation inhomogeneity increases with severity of COPD.[19,20]

When conducted as SPECT, the perfusion scan may exhibit the so-called "stripe sign," which is a central reduction in perfusion with preserved function peripherally in lung regions with centrilobular emphysema (Fig. 3).[16] In patients with severe COPD, many lung areas with the stripe sign concurrently show signs of centrilobular emphysema on HRCT, but in up to 15% of the areas, no specific changes can be detected using the latter.[16,21] If the SPECT is performed at breath-hold, the resolution furthermore increases, and the majority of patients will exhibit more extended perfusion defects than can be detected on CT.[22]

When using inert gases as ventilation tracers, the stripe sign is also evident on the ventilation scan, but when using Technegas, some areas may be stripe-sign positive on perfusion SPECT but negative on ventilation SPECT, because Technegas tends to deposit in the central airways (Fig. 2).[22] In contrast, the stripe sign is never observed in patients without COPD,[16,21] thus indicating that its presence signifies the presence of centrilobular emphysema, and since it may occur without any changes on HRCT, that V/Q SPECT is more sensitive for detecting early or mild emphysematous changes than HRCT.

Due to the critical importance of the distribution of ventilation relative to perfusion in the pathophysiology of COPD as outlined above, some SPECT-based studies have specifically assessed the distribution of the V/Q ratio and related indices in the lungs of COPD patients, and automated methods for doing this have been developed.[15,23] Studies have thus shown that COPD is associated with a very inhomogeneous distribution of the V/Q ratio throughout the lungs, a pattern that worsens with each GOLD category, and correlates with the impairment of pulmonary gas exchange determined by arterial blood gases.[23] This approach furthermore appears to be more sensitive at detecting emphysematous lung areas than compared to HRCT.[23]

Together, the available studies thus indicate that both the visually based and the more objective automatic approaches of lung scintigraphy have prospects for early detection and phenotyping of COPD, particularly when using SPECT rather than planar scans, while also using inert gases or Technegas rather than aerosols as ventilation tracers.

## Early Detection of COPD

As outlined above, the early pathophysiological events in COPD involve changes in pulmonary vascular function and structural changes in the small airways, neither of which are detected by spirometry or HRCT. Accordingly, studies of tobacco smoke-induced emphysema in mice have shown that the regional distribution of ventilation and perfusion assessed by SPECT is rendered more inhomogeneous in areas

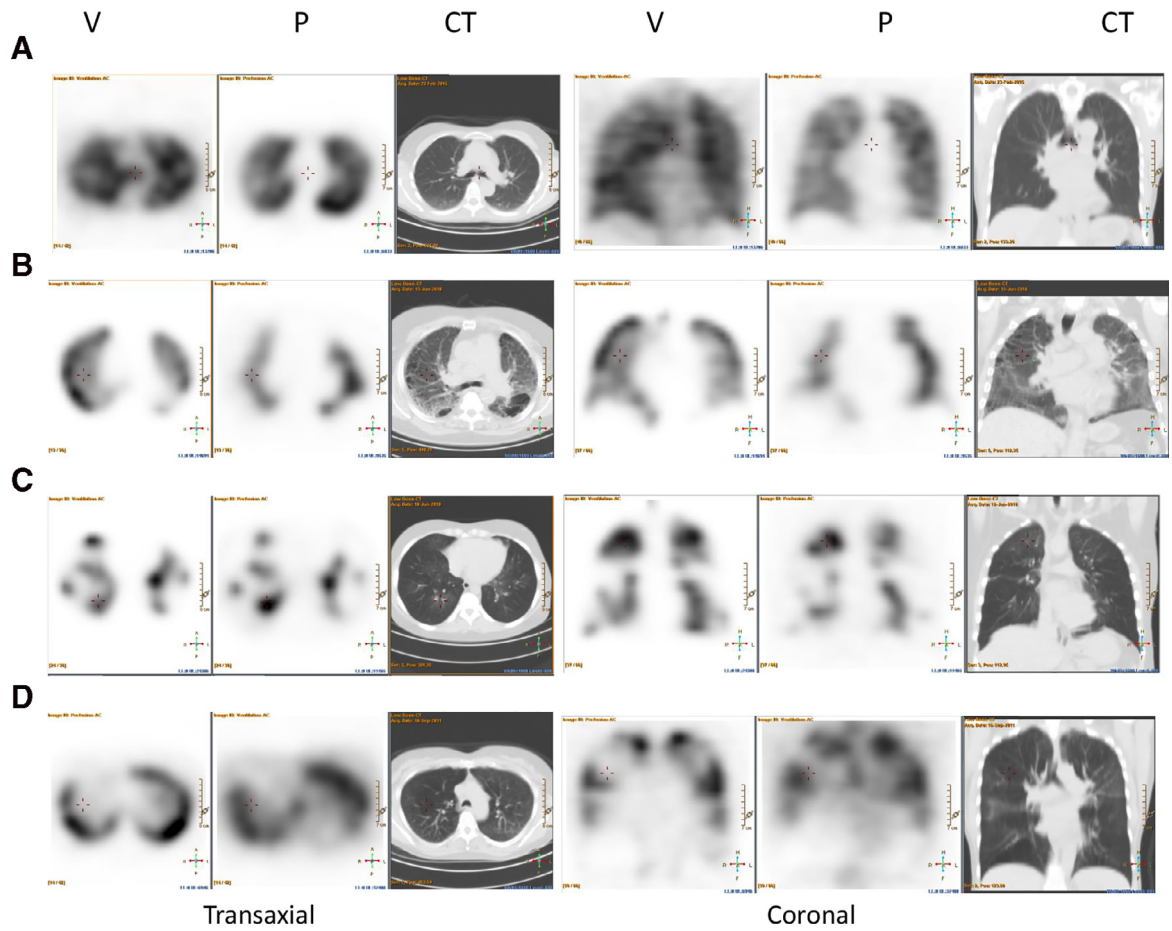


**Figure 1** V/Q SPECT/CT in COPD with and without emphysema and in a healthy volunteer. (A) V/Q SPECT/CT with mildly inhomogeneous ventilation and perfusion, and normal low dose CT findings in a middle-aged healthy volunteer with normal lung function. (B) Mismatch in mixed emphysema and fibrosis. Abnormal V/Q SPECT/CT with ventilation to the periphery and perfusion to the central part of the lobes. Right/left lung distribution of perfusion: 50/50%; ventilation: 64/36%. Patient with restriction and severely reduced DLco. HRCT shows extensive paraseptal and centrilobar emphysema (14% emphysema) and basal fibrosis. (C) Triple match in small airways disease. Severely abnormal V/Q SPECT/CT with multiple matched patchy ventilation and perfusion defects and matching with areas of mosaic perfusion on low-dose CT in subject with severe airway obstruction, hyperinflation, and reduced diffusion capacity due to bronchiolitis obliterans. HRCT shows extensive areas with low attenuation and mosaic "perfusion" and extensive air-trapping compatible with bronchiolitis obliterans, but no emphysema. (D) Triple match in emphysema. Severely abnormal V/Q SPECT/CT with matched reduced ventilation and perfusion which is worst in the lower part of the lungs matching with CT findings of emphysema (30% emphysema). Patient with severe airway obstruction, hyperinflation, and low diffusion capacity due to emphysema and alpha-1 antitrypsin deficiency. Left 3 images—transaxial projections. Right 3 images—coronal projections. Left: ventilation ($^{81m}$Kr); mid: perfusion; right: low-dose CT. COPD, chronic obstructive pulmonary disease; HRCT, High-resolution CT; V/Q, ventilation-perfusion.

with evidence of inflammation and airspace enlargement on histology, notably the small airways.[24] Since these changes are reversed by the cessation of tobacco-smoke exposure,[25] they likely reflect changes that also occur during the very early stages of COPD in the clinical setting. This may be detected as an inhomogeneous distribution of ventilation, as reported using ventilation SPECT in otherwise healthy smokers with normal spirometry.[19] While spirometry is not a sensitive measure of small airway function, studies that compare the results of V/Q SPECT to more specific and sensitive tests of small airway function, such as impulse oscillometry and multiple breath $N_2$ washout, are warranted, particularly in patients with early or mild COPD. Apart from ventilation inhomogeneity, such studies should also focus specifically on perfusion and V/Q ratio distribution patterns.

## Ventilation and Perfusion Scintigraphy in Lung Volume Reduction

In end-stage COPD, lung volume reduction using surgery or endoscopic treatments with one-way valves or coils may be used therapeutically to reduce the extent of emphysematous hyperinflation. This both improves the elastic recoil of the lungs and pulmonary gas exchange while also reducing dyspnea by shifting volume, ventilation, and perfusion from the most afflicted emphysematic lung lobes to better functioning areas. Both V/Q scintigraphy and CT are used to select eligible patients for the specific treatments, and are furthermore useful for identifying the most diseased target areas in the lungs and to assess treatment effects (Fig. 4).[26]

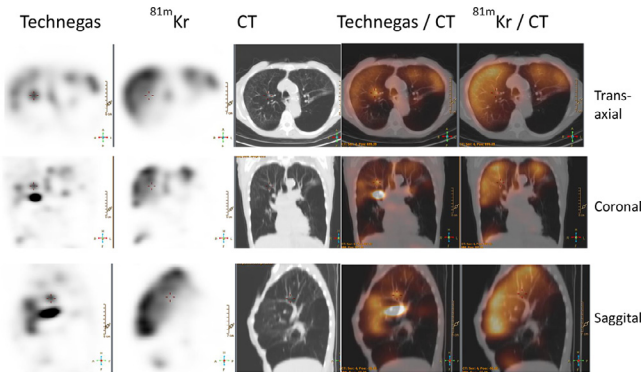


**Figure 2** Ventilation SPECT/CT with simultaneous acquisition of Technegas and $^{81m}$Kr-gas in a patient with severe COPD with emphysema. The krypton gas has a much more peripheral penetration and more homogenous distribution compared to Technegas, which shows several hot spots in the central airways. The ventilation is severely impaired in the lower lobes that are hyperinflated on CT. Patient has alpha-1 antitrypsin deficiency. Upper row—transaxial. Second row—coronal. Third row—saggital. Left: Technegas; left-mid: $^{81m}$Kr; center: low-dose CT; right-mid: fused Technegas/CT; right: fused $^{81m}$Kr/CT. COPD, chronic obstructive pulmonary disease; HRCT, High-resolution CT; V/Q, ventilation-perfusion.

A study showed that information obtained from planar perfusion scintigraphy combined with CT was superior to a CT-based assessment alone for determining the extent and distribution of emphysema prior to surgical lung volume reduction.[27] The ability of planar V/Q scintigraphy (using $^{81m}$Kr as the ventilation tracer) to predict outcome after lung volume reduction surgery was assessed in a prospective study on 50 patients with severe emphysema.[28] Both measures of ventilation and perfusion inhomogeneity predicted the postsurgical improvement in lung function evaluated by spirometry, and could furthermore largely explain why greater improvements were observed in patients with centrilobular than panlobular emphysema, as determined histopathologically in the resected specimens.[28]

The predictive impact of presurgical perfusion scintigraphy in relation to lung volume reduction surgery has been addressed in one retrospective study.[29] Both planar and SPECT perfusion scans were visually analyzed on a four-point scale in upper and lower lung zones to provide a specific perfusion index. This correlated to spirometry findings 3-12 months after surgery, and the results did not differ between planar imaging and SPECT, most probably because of the rather crude lung zones used. Hence, more advanced analyses, including a semiautomatic lobar analysis of V/Q SPECT/CT compared before and half year after treatment with endobronchial one-way valves showed significant reductions in perfusion, ventilation and volume of the treated lobes, and significant increases in the ipsilateral non-targeted lobes, but no changes in the contralateral lung.[30] In contrast, no changes were found using a crude 3-zone (upper, mid, lower) analysis of planar V/Q imaging, even though the intraobserver coefficient of variation for assessment of lobar target ventilation and perfusion was below 1% in planar analysis, and below 3% in SPECT/CT analysis.

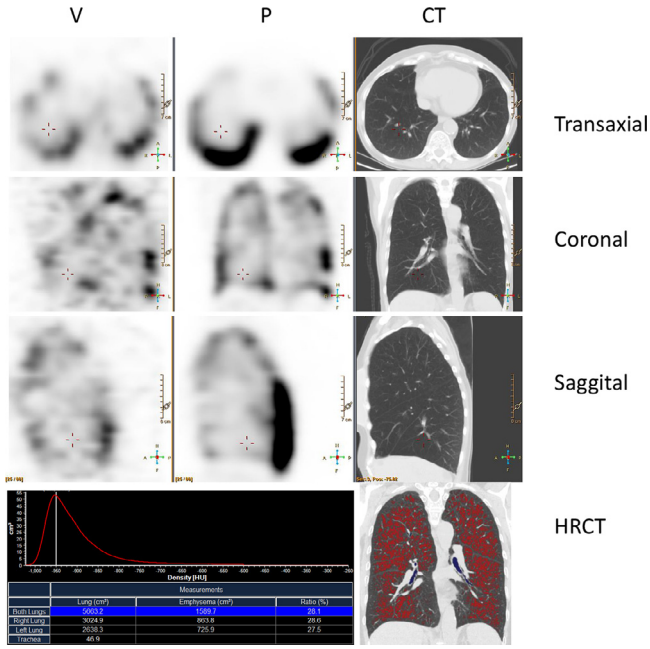


**Figure 3** V/Q SPECT/CT showing the stripe-sign in a patient with severe COPD with emphysema. Both ventilation and perfusion is primarily localized in the periphery (stripe-sign) with severe reduction in central parts of the lobes corresponding to centrilobular emphysema on HRCT (28% emphysema). Upper row—transaxial. Second row—coronal. Third row—saggital. Lower row: density map histogram and image of HRCT with emphysema marked red. Left: ventilation ($^{81m}$Kr); mid: perfusion; right: low-dose CT. COPD, chronic obstructive pulmonary disease; HRCT, High-resolution CT; V/Q, ventilation-perfusion.

The combination of CT and scintigraphy is thus useful for assessing patient eligibility, for identifying target zones, and for follow-up in the context of lung volume reduction treatment. However, the added value from using SPECT or SPECT/CT rather planar imaging, as well as from performing V/Q scintigraphy rather than a perfusion scan alone, remains to be clarified.

## Lung Scintigraphy, Comorbidities, and Complications of COPD

COPD patients have a high risk of serious complications and comorbidities such as exacerbations, pneumonia, pulmonary embolism, lung cancer, and cardiac failure. In addition to any COPD-related changes in ventilation and perfusion, these conditions may give rise to different characteristic patterns on V/Q SPECT.[31] In this context, adding a low-dose CT to a V/Q SPECT protocol is particularly useful. This approach was evaluated prospectively in stable COPD patients and healthy smokers,[32] in which the low-dose CT was found to make the V/Q SPECT interpretation more certain in 10% of the cases, while also providing additional diagnoses such as lung cancer, emphysema, pulmonary embolism, and heart failure, in the majority of cases. Hence, V/Q SPECT/CT has an added value compared to performing V/Q SPECT in COPD patients.

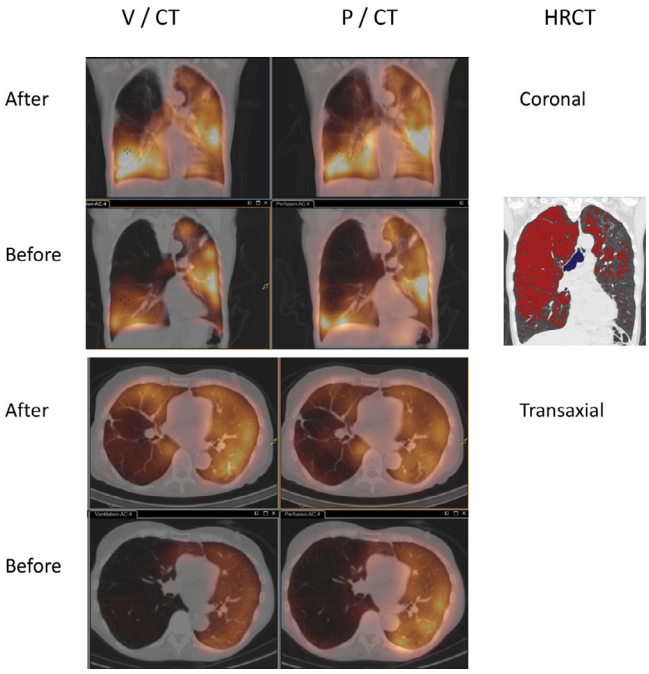


**Figure 4** V/Q SPECT/CT in a patient with severe COPD with emphysema before and after lung volume reduction surgery. Severe reduction of ventilation and perfusion in the upper part of right lung corresponding to centrilobular emphysema seen on HRCT. After lung volume reduction surgery of the right upper lobe, ventilation, and perfusion improves in the right lung which also is less hyperinflated. Left: fused ventilation ($^{81m}$Kr)/CT; mid: fused perfusion/CT. Right: HRCT with red marking of emphysema (47% emphysema; 62% in right and 20% in left lung). COPD, chronic obstructive pulmonary disease; HRCT, High-resolution CT; V/Q, ventilation-perfusion.

## Conclusion

V/Q scintigraphy is a valuable functional imaging biomarker in relation to several aspects of COPD. Disturbances in the distribution of ventilation and perfusion, which are pertinent to the pathophysiology of COPD, are directly visualized, particularly when using inert gases or Technegas as ventilation tracers while performing the scintigraphy as a SPECT. It is well documented that specific changes on V/Q scintigraphy reflect disease severity in COPD, and furthermore provide information on the extent and distribution of disease in the lungs. It is therefore important in the workup of lung volume reduction treatment, and when combined with low-dose CT it may furthermore add important information on complications and comorbidities of COPD. The high sensitivity of V/Q scintigraphy, particularly SPECT, may unveil very early and/or mild changes of COPD in the small airways and pulmonary vascular function that cannot be detected by spirometry or HRCT, but more clinical studies are warranted to determine its potential for the early detection of COPD.

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