Effects of ambient pressure on pulmonary nitric oxide

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Ever since nitric oxide (NO) was discovered in exhaled gas (11), there have been suggestions that pulmonary NO may have a role in the control of pulmonary blood flow. Indeed, Frostell et al. (10) demonstrated that inhaled NO could alleviate pulmonary hypertension in a sheep model. This notion has been supported by experimental evidence by, for example, Lundberg et al. (19) in humans and by Vaughan et al. (26) in an animal model, both without pulmonary hypertension. Pulmonary NO has also been implicated in the development of high-altitude pulmonary edema; Duplain et al. (8) and Busch et al. (3) showed that hypoxia decreased exhaled NO in mountaineers susceptible to this condition. Along the same line of thought, Erzurum et al. (9) showed that higher blood flow and circulating NO products offset high-altitude hypoxia among Tibetans.

Seemingly in contradiction to the suggested role of NO availability to the lung circulation at altitude with low gas density, experiments with inhalation of low-density gas at sea level have shown decreased levels of exhaled NO fractions (FENO) and partial pressures (PENO) (17, 23). During simulated altitude, we recently found that the exhaled NO partial pressure (PENO) for a given exhaled flow measured at standard temperature and pressure dry (STPD) was markedly reduced at altitude and more so with increasing altitude (12). This reduction in PENO was not caused by the hypoxia of air breathing at altitude, since an equivalent hypoxia under normobaric conditions did not significantly reduce PENO. We suggested that the reduced PENO was caused by enhanced backdiffusion of NO (25), which in turn would be caused by the reduced gas density at high altitude. In fact, the diffusing coefficient for NO in air varies inversely proportional to the ambient pressure (4). The altitude data (13) were obtained with a simple, handheld NO analyzer, and data were obtained for only one exhaled flow rate, which at altitude had to be corrected for deviating flow using empirical algorithms (12). Thus no data were obtained for parameters such as alveolar and conductive airway contributions to the exhaled NO. To perform a more detailed study on the effects of gas density and ambient pressure on pulmonary NO, we studied healthy individuals at a much wider range of ambient pressures and gas densities than before. Furthermore, we determined exhaled NO at different exhaled flow rates, permitting us to estimate alveolar NO and the contribution to exhaled NO from the conducting airways. Finally, we made all experiments during normoxia (inhaled PO2 of 21 kPa, 160 mmHg) to avoid any confounding influences of hypoxia in hyperbaric environment and hypoxia in hypobaric environment. We hypothesized that for a given exhaled volume flow an impaired diffusive transport of NO in a hyperbaric environment would increase the partial pressure differences for NO between the conductive airway compartment and the alveolar compartment, and that the reverse would occur with enhanced diffusive transport at altitude. We further hypothesized that there would be a lowered exhaled fraction of exhaled NO (FENO) due to a more marked dilution in a hyperbaric environment and a higher than normal fraction at altitude, attributable to less dilution of the NO formed in the airways. The final outcome on PENO of the interaction between dilution on one hand and backdiffusion on the other, at raised and lowered ambient pressures, remained to be determined experimentally.

METHODS

Subjects. Ten subjects volunteered for the study. They declared themselves healthy nonsmokers without a history of inflammatory airway disease. They came to the laboratory on three occasions, once for familiarization, spirometry, baseline FENO, and physical examination, and twice for experiments in increased or decreased ambient pressure in a combined hyperbaric and hypobaric pressure chamber.
Their exhaled NO fraction ($F_{ENO}$) and partial pressure ($P_{NO}$) at an exhaled flow of 50 ml/s BTPS were determined at normal ambient pressure on each occasion. Below, the term $F_{ENO}$ and the corresponding partial pressure ($P_{ENO}$) refer to those at an exhaled flow of 50 ml/s BTPS if not stated otherwise. The subjects were instructed to abstain from nitrate- and nitrite-rich food for 12 h before each session. In two subjects, both baseline $F_{ENO}$ and variability between experimental days exceeded the normal ranges recommended in current medical practice guidelines (1). Therefore, their data were not used. The remaining eight subjects, four women, completed all tests at three different ambient pressures and had stable baseline $F_{ENO}$ over time. Their age, height, and weight ranged 21–37 yr, 1.60–1.93 m, and 58–87 kg, respectively. The experimental protocol was approved by the Regional Ethical Review Board in Stockholm, and subjects gave written informed consent to participate.

**Procedures.** Experiments were performed at 505 ± 0 (mean ± SE), 1,015 ± 3, and 4,053 ± 0 hPa ambient pressure. The corresponding values (in mmHg) were 379, 761, and 3,040. The pressure chamber (internal volume 8 m$^3$) was pressurized with air, but subjects breathed normoxic gas mixtures with oxygen fractions of 0.421, 0.2095, and 0.052 at 505, 1,015, and 4,053 hPa, respectively. Subjects were investigated at hypobaric and hyperbaric pressures on different days and in random order. Each experimental day started with a full set of $F_{ENO}$ measurements at normal pressure and then a full set at increased and reduced pressure. A full set of measurements included duplicate $F_{ENO}$ measurements at three to four different flows and in random order. After a change in ambient pressure, a 15-min waiting time was allowed to accommodate to the new environment while breathing the normoxic gas mixture. Subjects rinsed their mouths with water prior to each series of $F_{ENO}$ measurements. Decompression after the hyperbaric experiments was performed according to Swedish Navy standard tables and with correction for the increased nitrogen partial pressure compared with air breathing. There were no decompression symptoms in any of the subjects. Two subjects at a time were studied, with one supervisor inside the chamber and two on the outside.

**Instrumentation and measurements.** Subjects were breathing through an oronasal mask and a nonbreathing valve (Hans Rudolph, Shawnee, KS) from a 200-liter Douglas bag via 40 mm internal diameter hoses. The supervisor kept the bag adequately filled by through the chamber wall and to the inlet of a chemiluminescence NO analyzer (Sievers Nitric Oxide Analyzer 280, GE Analytical Instruments, Boulder, CO). Gas for CO$_2$ analysis was sampled in a similar manner to a mass spectrometer (Innovision A/S, Odense, Denmark). The analyzers were calibrated with certified gas mixtures with 200 ppb NO in nitrogen and 1.0.5, and 10.0% CO$_2$, respectively (AGA SpecialGas AB, Lidingö, Sweden). These gases were sampled from the inside of the chamber. Also, the output from the gas analyzers was fed to the digital data-acquisition system. There was an ~300 ms sample delay in the NO analysis. Despite the large differences in upstream sampling pressure between conditions, there was only a 30% difference in signal output between 505 and 4,053 hPa for a given calibration gas.

**Data analysis.** For each subject, a set of calibrated values for exhaled NO and exhaled flow were collected. NO data were converted from fraction to partial pressure and exhaled flows were converted from BTPS to STPD, using standard algorithms. For each subject, plots were made of $F_{ENO}$ and $P_{ENO}$ vs. 1/exhaled flow (STPD and BTPS, respectively). Estimates of alveolar NO partial pressure ($P_{ANO}$) were obtained from the Y intercept of plots of $P_{ENO}$ vs. 1/flow STPD, and estimates of the conductive airway contribution to exhaled NO were obtained from the slopes of the linear plots of $P_{ENO}$ vs. 1/flow STPD (22). Interpolation in plots of $F_{ENO}$ and $P_{ENO}$ vs. 1/flow BTPS was used to compute $P_{ANO}$ at an exhaled flow of 50 ml/s BTPS, according to the present clinical standard (1), and its counterpart was expressed as partial pressure.

**RESULTS**

Figure 1, A–D, shows data from one typical subject when plotted as described above. Basically, one single plot and with appropriate conversion of units could be used to derive all parameters such as $P_{ANO}$, $J_{AWNO}$, $F_{ENO}$, and $P_{ENO}$, but all four plots are shown here for clarity.

Figure 2, A and B, shows group mean values for $J_{AWNO}$ and $P_{ANO}$. $J_{AWNO}$ (Fig. 2A) did not differ significantly between 505 and 1,015 hPa (control) but was 21% lower at 4,053 hPa than during control ($P = 0.009$). Figure 2B shows group mean values of $P_{ANO}$, obtained from the intercept of the y-axis, as shown in the example in Fig. 1B. $P_{ANO}$ differed markedly between conditions; at 505 hPa it was 88% of control ($P = 0.04$) and at 4,053 hPa it was 176% of control ($P = 0.009$).

Figure 3, A and B, shows $F_{ENO}$ and $P_{ENO}$. $F_{ENO}$ (Fig. 3A) differed widely between pressures, with the highest values at 505 ($< 0.0001$) and the lowest at 4,053 hPa ($< 0.0001$) compared with control. In contrast, $P_{ENO}$ values were practically identical between the three pressures (Fig. 3B).

Figure 4, A and B, shows the differences between $P_{ENO}$ and $P_{ANO}$ (Fig. 4A) together with the product between this difference and the diffusivity of NO in the breathing gas (Fig. 4B). The $P_{ENO} - P_{ANO}$ difference was essentially the same at 505 hPa and control and was 82% of control at 4,053 hPa ($P = 0.016$). The product of this difference and the diffusivity differed markedly between conditions from 208% of control at 505 hPa ($P = 0.0001$) to 21% of control at 4,053 hPa ($P < 0.0001$).

End-tidal CO$_2$ between the $F_{ENO}$ maneuvers averaged $4.37 ± 0.15, 4.47 ± 0.18,$ and $4.62 ± 0.23$ kPa at 505, 1,015, and 4,053 hPa, respectively, with no significant difference between pressures.

**DISCUSSION**

Several findings in this study were unexpected; one would intuitively assume that with increased gas density and decreased diffusivity for NO in the background gas, the exhaled portion of the NO formed in the conductive airways would be increased and the backdiffusion portion would be correspondingly decreased. Along the same line of thought, one would
expect lowered PENO values at 505 hPa (17, 23) compared with control and increased PENO at 4,053 hPa. Instead we found strikingly similar PENO values at the three pressures. Also, the apparent JawNO values would be expected to increase with pressure but, in fact, the opposite was found. Finally, the alveolar estimates were contrary to expectations, because enhanced backdiffusion would be expected to lead to increased PANO values at simulated altitude and decreased PANO in hyperbaria. The present findings should be understood as a result of an interaction between the flow-dependent dilution of the NO in the airways, the density-dependent conditions for

Fig. 1. Exhaled NO as a function of the inverse of the exhaled flow at three different ambient pressures in a typical subject. A: 505 hPa; B: 1,015 hPa (sea level); C: 4,053 hPa. A: fraction of exhaled NO (FENO) as a function of 1/exhaled flow at body temperature and pressure, saturated with water vapor (BTPS). B: exhaled NO partial pressure (PENO) as a function of the same quantity as in A. C: FENO as a function of 1/exhaled flow at standard temperature and pressure dry (STPD). D: PENO as a function of the same quantity as in C.

Fig. 2. A: contribution from conductive airways to the exhaled flux of NO (JawNO) at 3 different ambient pressures. Data are mean values and SE (vertical bars) from 8 subjects. B: estimated alveolar NO partial pressure (PANO) at 3 different ambient pressures for the same subjects.

Fig. 3. A: FENO at a flow of 50 ml/s BTPS. B: PENO at the same exhaled flow as in A. See Fig. 2 for explanations.
Partitioning between exhaled NO and backdiffusion NO. In a classical two-compartmental analysis (6), the NO formed in conducting airways appears only partly in the exhaled air. Indeed, models including NO transport by diffusion have shown that the remainder is transported by backdiffusion to the alveoli and then is taken up by the blood (17, 23, 24). The present data with decreased apparent $J_{awNO}$ in hyperbaria could have three possible explanations: either the backdiffusion is increased rather than decreased, or there is an additional backtransport mechanism, or the rate of transfer of NO from the airway epithelium into the gas is attenuated.

To be able to assess the conditions for backdiffusion of NO (25), the two main variables of Fick’s first law of diffusion must be established, namely the partial pressure difference along the distance of diffusion and the diffusivity of NO in the background gas. The diffusion coefficients are known, are inversely proportional to the ambient pressure, and are 0.44, 0.22, and 0.055 cm$^2$/s, respectively (4). We have estimates of $P_{ANO}$ and a characteristic value for the conductive airway $P_{ENO}$ at each of the ambient pressures. Let us for a moment, and for the sake of simplicity, assume that the overall rate of NO formation in the conducting airways ($J_{awNOtot}$) is the same at the three pressure conditions. Let us further adopt a standard value of 0.75 as the fraction of $J_{awNOtot}$ that is found in the exhaled gas (apparent $J_{awNO}$) at normal ambient pressure (1,013 hPa) and exhaled flow (50 ml/s BTPS) (18) and that this fraction varies in proportion to the product between the (PE – PA) difference and the diffusivity. Rough average estimates for backdiffusion would then be 284, 137, and 28 pl/s for 505, 1,015, and 4,053 hPa ambient pressures, respectively, based on the present apparent $J_{awNO}$ values and using the assumed backdiffusion at 1,015 hPa as a reference (Fig. 5). Applying a model assuming constant $J_{awNOtot}$ and backtransport driven by the product between the PE – PA difference and the diffusivity for NO, the data that are obtained for 505 and 4,053 hPa contradict the basic assumptions of the model (Fig. 5). Thus backtransport at 505 hPa comes out so large that the sum of apparent $J_{awNO}$ and backtransport markedly exceeds the assumed constant $J_{awNOtot}$. For 4,053 hPa, the corresponding sum comes out substantially lower than the assumed constant $J_{awNOtot}$. In this comparison of data between pressures, the molecular flow of the background gas during the whole $F_{ENO}$ maneuver is half of that during control at 505 hPa (19 ml/s STPD) and four times increased at 4,053 hPa (173 ml/s STPD).

A tentative way to reconcile this conflict between model assumptions and outcome when using experimental data would be to consider a second mechanism for backtransport apart from diffusion that is also influenced by differences in ambient pressure and gas density. Such a mechanism has been proposed for the oxygen transport within the peripheral airways; Martin et al. (20) found that the alveolar-arterial oxygen partial pressure differences [(A-a)DO$_2$] were reduced compared with normobaric air controls in dogs being ventilated with a high-density oxygen-sulfur hexafluoride mixture at 4 atmospheres. Johnson and Van Liew (15), showed that oxygen wash-in after
breath-holding was faster with a nitrogen-oxygen mixture than with an equally normoxic helium mixture of much lower density. Furthermore, Wood et al. (27) found reduced \((A-a)\text{DO}_2\) in humans breathing 21% oxygen in sulfur hexafluoride, compared with air controls. All authors concluded that the denser gas improved oxygen transport by causing a more optimal distribution of inspired gas. Paiva and Engel (21), proposed a theoretical analysis of this phenomenon based on the concept that the denser gas moved the diffusion front for oxygen transport more toward the periphery. This notion was further supported by Christopherson and Hlastala (5), who described the phenomenon as an “interaction between diffusion and convection on inspiration.”

In Fig. 6 we show conceptually the outcome with a revised model in which there are dual mechanisms for backtransport: one diffusive and one convective. As before, the diffusive component is proportional to the product between the PE – PA difference and the diffusivity, but now we assume that this component is only 40% of the total backtransport at 1,015 hPa. This percentage is not critical; conceptually similar outcomes are obtained within the range 30–70%. The convective component is assumed to make up the difference so to obtain a constant JawNOtot across pressures. The model suggests that the convective component of backtransport increases with increasing pressure, gas density, and increasing STPD flow. It could be argued against the proposed analog between oxygen transport and backtransport of NO in the lung periphery that alveolar uptake of oxygen is perfusion dependent, whereas the NO uptake in a strict sense is not. However, NO uptake to the blood depends on the size of the area of the gas-blood interface, which in turn varies in concert with perfusion (16).

In summary, therefore, our experimental data would fit into a model in which ambient pressure and gas density influences backtransport of NO in two opposite ways: one diffusive component that is attenuated and one convective component that is enhanced with increasing pressure and gas density.

**Possible effects of ambient pressure on JawNOtot.** The proposed model rests on the assumption that JawNOtot is constant across ambient pressures. An alternative explanation for our finding of a significantly reduced apparent JawNO at 4,053 hPa compared with control would be a corresponding reduction of JawNOtot, for which there are several tentative mechanisms to consider, including diffusion across the epithelial-airway interface, respiratory mechanics, and metabolic feedback.

The NO partial pressure inside the NO-forming epithelium has been proposed to be 150 mPa, corresponding to 1,500 ppb of an atmosphere (24), compared with the present luminal PNO in the conductive airways of less than 2% of that value and practically identical across pressures. Therefore, it is not likely that small differences of airway PNO between pressure conditions, if any, could cause the observed 21% reduction of JawNO (Fig. 2A) by influencing diffusive transport across the epithelial-airway interface.

A further mechanism to consider is a possible impact of mechanical stimuli on JawNO. Bannenberg and Gustafsson (2) showed that increased end-expiratory pressure and airway pressure vibrations could enhance JawNO in a rabbit model. Although respiratory mechanics are markedly different between the present two higher pressures during maximum breathing efforts, respiratory mechanics during resting breathing are not significantly different within the present range of pressures (14).

An interesting aspect is to compare the behavior of pulmonary NO with another metabolic gas, namely carbon dioxide (CO₂). CO₂ is formed in the body at a relatively constant rate and is eliminated through the lungs. In resting humans, pulmonary ventilation, traditionally quantified in liter per minute BTPS, is constant within the present range of ambient pressures and gas densities, if conditions with the same inspired oxygen partial pressure are compared (7, 14). The partial pressures of mixed exhaled and alveolar PCO₂, respectively, are therefore also the same at these pressures, and the fractions are consequently inversely proportional to ambient pressure. This was indeed true for the present estimates of alveolar PCO₂ and this is the same behavior as we observed for NO in the present study. A constant exhaled flow in BTPS units across pressures can be regarded as an analog to the constant pulmonary ventilation prevailing in resting humans in the same pressure range and in the absence of hypoxia or hyperoxia. Thus it appears as though NO behaves like a metabolic gas with a tightly controlled production and, therefore, also an equally constant partial pressure at the same BTPS ventilation/exhaled flow across a wide range of ambient pressures. If true, this would be a tentative mechanism by which JawNOtot could be indirectly influenced by ambient pressure and gas density; a tendency for decreased backdiffusion and increasing airway PNO would then impede epithelial NO production by a feedback mechanism and restore a target PNO level.

**Comparisons with earlier results.** The present results are in agreement with a previous study of exhaled NO at simulated

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**Fig. 6.** Model computation assuming 3 components of JawNOtot. Solid part of bars, apparent JawNO, same as in Fig 5. Open part, backdiffusion as 40% of that in Fig 5. Shaded part, postulated convective component, making up the remainder of an assumed constant JawNOtot of 549 pl/s STPD. See Figs 2 and 5 for explanations.
altitude. Hemmingsson and Linnarsson (13) compared hypoxic gas breathing at sea level with air breathing at a pressure equivalent to 5,000 m altitude and with the same inspired partial pressure of oxygen in the two conditions. The paper reports \( P_{ENO} \) values for a given STPD flow, but data could be converted to those for the same BTPS flow at the two pressures using algorithms proposed earlier by the same authors (12). Data so converted show \( P_{ENO} \) values at the two pressures that are practically identical between conditions, just as in the present study. Our results are, however, at variance with two previous studies using helium-oxygen breathing before and during \( F_{ENO} \) determination to increase the diffusivity for NO in the lung gas. Shin et al. (23) had their subjects breathe a helium-oxygen mixture for 2 min and found a 45% decrease of \( P_{ENO} \) compared with air breathing. Kerckx et al. (17) found a 36% decrease using a similar technique. The authors report diffusivities of 0.52 and 0.6 cm/s, respectively, with helium-oxygen compared with 0.22–0.23 cm/s with air at normal pressure, to be compared with the present diffusivity at 505 hPa of 0.44 cm/s. Theoretically, an increased diffusivity should have the same impact on intrapulmonary diffusion regardless of if it is obtained with a gas of low molecular mass, such as helium, or by reducing the ambient pressure. Neither of the two studies report data for \( F_{ANO} \) and \( Jaw_{NO} \) with helium-oxygen, which would have permitted a more detailed comparison with the present altitude data.

A tentative explanation for this discrepancy of results between the present and those from helium-oxygen breathing could be sought in clear differences in the duration of low-density gas breathing. The present subjects spent at least 1 h at altered pressure at a time, so on the average a \( F_{ENO} \) measurement was preceded by 38 min of low-density gas breathing and never less than 15 min. In addition, the density change was instantaneous with the arrival at the new pressure. In the two studies with helium-oxygen breathing there were 2 min of wash-in of low-density gas before measurements, which likely took most of this time period to become reasonably completed. To our knowledge, there are so far no studies of the time course to reach a new steady-state NO turnover in the lungs after a change in gas density, so for now, the potential impact here of the time factor remains open to speculation.

**Estimates of alveolar NO.** The alveolar \( P_{NO} \) values were found to increase significantly with ambient pressure and decreasing diffusivity for NO in the background gas (Fig. 3B). This finding suggests that the \( P_{ANO} \) estimate obtained by extrapolation to 1/flow = 0 may not necessarily represent gas samples from the immediate vicinity of the gas-blood interface. An alternative interpretation of these data could therefore be that they represent gas from an intermediate position between a peripheral site of NO formation and the gas-blood interface. If so, it might be expected that diffusive transport dominates the most distal part of the pathway for backtransport and that convective mechanisms have an impact on the proximal part. In such a way, increased density may promote backtransport in the proximal part and at the same time impede backtransport in the distal part. Such a mechanism would be compatible with the present findings of increased alveolar NO (\( P_{ANO} \)) estimates with increased gas density.

**Practical consequences for exhaled NO measurements at different ambient pressures.** Since conductive airway and exhaled \( P_{ENO} \) are flow/ventilation dependent, such a definition must take into account how ventilation is controlled. As already discussed above, the BTPS ventilation is constant across pressures at rest. Thus the prevailing \( P_{NO} \) in the airways will be that resulting from a set level of BTPS flow, preferably with 50 ml/s as a standard (1). If that is not technically feasible, we recommend that a multiple-flow technique is used so that \( P_{ENO} \) values for a given BTPS flow can be assessed by interpolation/extrapolation. As a third, but not recommended alternative, single-flow measurements can be treated with conversion algorithms like those described by Hemmingsson et al. (12). Finally, the present \( P_{ENO} \) results demonstrate that, in the absence of hypoxia/hyperoxia, the acute response to a reduced ambient pressure should be an inversely proportional increase of \( F_{ENO} \). The reverse seems to be true for an increase of ambient pressure. Thus measurements of \( F_{ANO} \) during, for example, an altitude study, will not be very informative, unless converted to partial pressure, and could be misleading if taken out of a proper context.

**Limitations.** The present study is limited to a comparison between acute exposures to different pressures and with normoxia. Thus the present findings should mainly be influenced by pressure effects acting through changes in diffusive and possibly also convective transport of NO. The effects of simulated altitude described here will not necessarily be the same as those observed with more extended exposures to high altitude, including extended hypoxia.

Within the relatively short (30–40 min) exposure to hypobaric or hyperbaric pressure, we saw no trend in which the order of identical measurements had an impact. We therefore believe that the present \( F_{ANO} \) and \( P_{ENO} \) values represent steady-state measurements at each pressure.

Ideally, we would have wanted to have identical sets of exhaled BTPS flows at the three pressures. However, since for a given partial pressure, the fraction (as measured outside the pressure chamber) is reduced by a factor of four at the highest pressure, it would have gone below the lower detection limit/accuracy range of our NO analyzer if we had used a higher exhaled flow than the present 127 ml/s BTPS.

**Conclusions.** With the present experimental design (0.5–4 ATA, normoxia, acute exposure), the exhaled NO partial pressure did not differ between ambient pressures, and consequently, the exhaled NO fractions varied in inverse proportion to the ambient pressure. Estimates of alveolar \( P_{NO} \) increased with pressure and were twice as large at 4 ATA as at 0.5 ATA. Our findings show that the response to an acute (0.5–1 h) exposure to a change in ambient pressure, gas density, and diffusivity is more complex than a mere change in the rate of backdiffusion of NO in proportion to the diffusivity of NO in the background gas. Taken together, our data on exhaled and alveolar \( P_{NO} \) suggest that convective backtransport of NO may play an increasing role with high-density gas and tend to compensate for an attenuated diffusive backtransport. On the other hand, our data on the exhaled NO flux (\( Jaw_{NO} \)) could also be a sign of pressure-induced suppression of the NO formation in the airways.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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