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Original Research

AGING

# Aging, Diabetes, and Hypertension Are Associated With Decreased Nasal Mucociliary Clearance

*Janaína Proença de Oliveira-Maul, MSc; Heráclito Barbosa de Carvalho, MD, PhD; Danielle Miyuki Goto, PhD; Raphaela Mendonça Maia, BSc; Claudia Fló, PhD; Viviane Barnabé, PhD; Denise Reis Franco, MD; Simon Benabou, MD; Monica Rodrigues Perracini, PhD; Wilson Jacob-Filho, MD, PhD; Paulo Hilário Nascimento Saldiva, MD, PhD; Geraldo Lorenzi-Filho, MD, PhD; Bruce K. Rubin, MD, MEngr, MBA, FCCP; and Naomi Kondo Nakagawa, PhD*

***Background:*** **We showed previously that nasal mucociliary clearance was decreased in critically ill elderly subjects, most of whom had diabetes mellitus (DM) and/or hypertension (HTN). To determine if these changes were due to the effects of aging, disease, or critical illness, we studied nasal mucociliary clearance and mucus properties in an ambulatory population consisting of young, elderly, and healthy subjects and those with DM, HTN, or both.**

***Methods:*** **Of 440 subjects contacted, 252 entered the study. The subjects were divided into the following groups: (1) healthy (n = 79, 18-94 years, 50 men) and (2) DM and/or HTN, of which 37 had DM (14-90 years, 12 men), 52 had HTN (23-90 years, 12 men), and 84 had both DM and HTN (25-82 years, 33 men). Subjects were also grouped by age: $<$ 40 years, 40 to 59 years, and $\geq$ 60 years. We assessed demographic and clinical data, quality of life using the 36-Item Short Form Health Survey (SF-36) questionnaire, nasal mucociliary clearance using the saccharine transit test (STT), and in vitro mucus properties by examining the sneeze (high airflow) clearability and contact angle. A logistic regression analysis for prolonged STT $>$ 12 min was used, and we controlled for age, sex, and diseases.**

***Results:*** **Subjects aged $>$ 60 years reported a decreased SF-36 physical component relative to other age groups. Sex, BMI, BP, heart rate, pulse oximetry, blood glucose level, and mucus properties were not associated with prolonged STT. Aging and DM and/or HTN independently increased the risk of prolonged STT.**

***Conclusions:*** **Aging and DM, HTN, or both diseases are independently associated with decreased nasal mucociliary clearance. This may predispose toward respiratory infections.**

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**Abbreviations:** DM = diabetes mellitus; HTN = hypertension; SF-36 = 36-Item Short Form Health Survey; STT = saccharin transit test

Pneumonia is one of the leading causes of death in the elderly.[1,2] Age-related changes in the respiratory tract,[3,4] such as decreased elasticity of the lung extracellular matrix, loss of diaphragmatic strength,[5] and declining lung function, may increase susceptibility to infections.[6] Mucociliary clearance is an innate defense mechanism of the respiratory tract against foreign microorganisms and particulates. Impaired mucociliary clearance has also been associated with respiratory infection.[7] We showed previously that nasal mucociliary clearance was decreased in the critically ill elderly.[8] Among the 16 critically ill subjects included in that study, 13 had diabetes mellitus (DM) and hypertension (HTN). These illnesses are prevalent in the elderly[9,10] and in youth,[11,12] and the disease or therapy may affect the respiratory immune function.[13] We could not determine if decreased mucociliary clearance was due to age, disease, or critical illness or if decreased nasal mucociliary clearance also occurred in the ambulatory chronically ill elderly. In the current study, we evaluated the effects of aging, alone and in combination with DM and/or HTN, on perceived quality of life, nasal mucociliary clearance, and the biophysical properties of mucus.

## Materials and Methods

### *Study Participants*

This cross-sectional study was approved by the local ethics committee (CAPPesq No. 802/07). The study population consisted of nonsmoking subjects, aged > 14 years, from four institutions and locations in São Paulo City: the Association of Juvenile Diabetes, the Outpatient Clinic of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, the Sports Center of the University of São Paulo, and the Elderly Center of São Paulo City. Subjects were invited by phone to participate in the study during 2009 and 2010. The purpose and procedures of the study were explained to all subjects and, in the case of adolescents, also to their parents. The subjects were included after they signed the written informed consent according to the Declaration of Helsinki of the World Medical Association.

Subjects each completed a health questionnaire, and their medical records were reviewed by a study physician. Subjects were considered healthy when they had not been given a diagnosis of or been treated for any chronic disease. The diagnoses of DM and HTN were made according to the American Association of Diabetes[14] and the American Association of Cardiology.[15] Subjects were excluded if they had a decreased level of consciousness, resided in a nursing home, were unable to understand and follow commands, had had previous nasal surgery, had had a respiratory infection in the 4 weeks before an assessment, or had had other respiratory disease.

Subjects were categorized as healthy subjects or as having DM and/or HTN. They were then subdivided into three age groups: < 40 years, 40 to 59 years, and ≥ 60 years.

### *Clinical Assessment*

A clinical history was taken, and the 36-Item Short Form Health Survey (SF-36) was administered. The SF-36 is a multidimensional scale consisting of eight dimensions that evaluate health-related quality of life.[16,17] Each dimension is measured on a scale from 0 (the worst health reported) to 100 (the best health). These dimensions were aggregated and shown as a physical component summary (physical functioning, physical role functioning, pain, and general health) and a mental component summary (vitality, social functioning, emotional role functioning, and mental health). A random blood glucose level was assessed, and heart rate, systolic and diastolic BP, and pulse oximetry were measured.

### *Saccharine Transit Time Test*

Clinical assessments were performed in a quiet room. Subjects were asked to avoid alcohol and coffee during the 6 h before their assessments. Because of circadian variation in mucociliary clearance, all assessments were performed between 2:00 PM and 6:00 PM.[18] Subjects who were able to taste saccharine deposited on their tongue were asked to report the first perception of a sweet taste after 25 mg of saccharine powder was deposited in the tested nostril.[8,19-24] The saccharine transit test (STT) results were recorded in minutes, with times of ≤ 12 min considered normal.[25-32] During the STT, the subjects were asked to maintain normal ventilation and to swallow freely but to avoid deep breaths, talking, coughing, sneezing, sniffing, eating, and moving. After 60 min, if the subject failed to taste saccharine, we repeated the STT the following day.[21]

### *Mucus Sample Collection and Analysis*

A mucus sample was collected using a soft brush placed gently in the opposite nostril from the side used during the STT.[22,25] The mucus sample was then removed from the brush, kept in a plastic tube, and stored at −70°C for later analysis. Airflow clearability was assessed using a machine designed to mimic the flow profile of a natural sneeze. The device had a gas cylinder of compressed air supplying 280 kPa of pressure, a gas-release solenoid valve to control the timed flow release at 0.5-s intervals, and a cylindrical acrylic tube with a 4-mm internal diameter and 133-mm length as an experimental nose model. The mucus sample was placed in the lower part of the acrylic tube, which was connected to the solenoid valve. Airflow clearability was quantified by determining the mucus displacement in millimeters.[22,25]

The contact angle of a sessile mucus droplet was measured using a stereo-microscope (Stemi 2000C; Carl Zeiss) connected to a camera (Axiocam HSC; Carl Zeiss) and to a microcomputer with an imaging program (Interactive AxionVison 4.7; Carl Zeiss).[33] Briefly, a small sample of mucus was placed on a glass slide that had been treated previously with a sulphochromic solution to remove electrical charges and then washed several times with deionized water.[34] Five minutes after deposition, the contact angle was measured in degrees.

### *Statistical Analysis*

Descriptive statistics are presented as means ± SD. The sex, BMI, SF-36 physical and mental component summary data, BP, heart rate, pulse oximetry, blood glucose, STT, mucus airflow clearability, and contact angle data are described for each age group (< 40 years, 40-59 years, and ≥ 60 years) in the healthy and the DM and/or HTN groups and were analyzed by two-way analysis of variance with post hoc correction by Bonferroni adjustment at the level of significance $P < .01$. All variables were tested with bivariate models ($\chi^2$ or $t$ test) as appropriate for data type and distribution to explore possible association with prolonged STT. The potential modifying factors were explored by logistic regression analysis (stepwise forward) using STT as a binary variable,

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**Affiliations:** From the Department of Physiotherapy, Communication Science and Disorders, Occupational Therapy, LIM 34 (Ms Proença de Oliveira-Maul and Drs Goto, Barnabé, and Nakagawa); the Department of Pathology, LIM 05 (Ms Proença de Oliveira-Maul and Drs Goto, Barnabé, Benabou, Saldiva, and Nakagawa); the Department of Preventive Medicine, LIM 39 (Dr Barbosa de Carvalho); the Department of Geriatrics (Drs Fló and Jacob-Filho); the Division of Pneumology (Dr Lorenzi-Filho), Heart Institute, Faculdade de Medicina da Universidade de São Paulo; Master of Science Program in Physiotherapy (Ms Maia and Dr Perracini), University of São Paulo City; and Associação de Diabetes Juvenil (Dr Franco), São Paulo, Brazil; and the Virginia Commonwealth University Department of Pediatrics (Dr Rubin) and Children's Hospital of Richmond at Virginia Commonwealth University (Dr Rubin), Richmond, VA.
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**Correspondence to:** Naomi Kondo Nakagawa, PhD, Faculdade de Medicina da Universidade de São Paulo, 455 Av. Dr. Arnaldo room 1150, Cerqueira Cesar, São Paulo, Brazil, CEP 01246-903; e-mail: naomi.kondo@usp.br

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prolonged when STT > 12 min. A *P* value < .05 was considered statistically significant.

## Results

### Demographic and Clinical Characteristics

Of the 440 subjects who were initially contacted by telephone, 252 agreed to participate and successfully completed the study (Fig 1). Of these 252 subjects, 79 were healthy. Among the remaining subjects, 173 had medical conditions (DM and/or HTN): 37 subjects had only DM, 52 subjects had only HTN and 84 subjects had both DM and HTN.

The frequency of having DM alone decreased with aging, whereas the frequency of HTN alone and both HTN and DM increased in older subjects. Not surprisingly, younger subjects had a higher prevalence of type 1 DM (87%), and elderly subjects had a higher prevalence of type 2 DM (52%). The likelihood of having only DM (n = 31) was greater in younger subjects (n = 21, 68%) compared with the other age groups, in part because many of the younger subjects were recruited from a diabetes clinic. Elderly subjects (n = 97) had HTN alone (n = 41, 42%) or both DM and HTN (n = 52, 54%) more often than did young subjects (13% and 19%, respectively). Fewer subjects over 60 years of age than those under 40 years used medications to control blood sugar (51% vs 87%, *P* < .001) but more used diuretics (35% vs 3%, *P* = .024), antihypertensives (74% vs 23%, *P* < .001), and β blockers (23% vs 0%, *P* = .015).

Older subjects who had DM and/or HTN had a higher BMI and BP and a lower SF-36 physical component summary (*P* < .001) than did healthy younger subjects (Table 1). There were no significant differences among age groups in oxygen saturation, heart rate, blood glucose levels, or SF-36 mental component summary score comparing healthy subjects and those with medical conditions (DM and/or HTN).

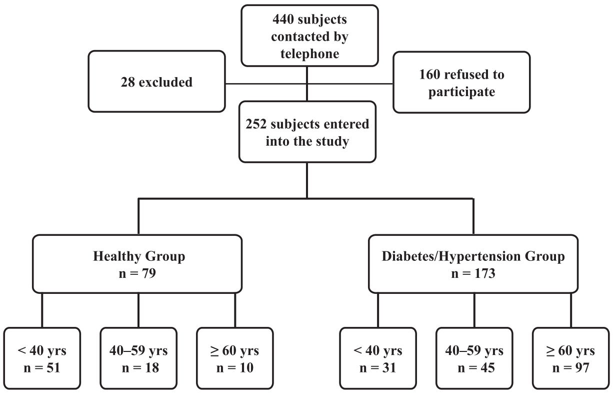


Figure 1. Scheme of recruitment, selection, and participation in the study.

### STT and Nasal Mucus Physical Properties

The STT was carried out accurately in all subjects. One healthy subject did not taste the saccharine on the first day, but the STT was conducted successfully the following day. Of the healthy subjects (n = 79), 81% had a normal STT, whereas approximately 50% of the subjects with medical conditions, particularly the elderly group, had decreased nasal mucociliary clearance (Fig 2).

BMI, sex, BP, pulse oximetry, blood glucose, and SF-36 results were not associated with prolonged STT (*t* test, *P* > .05). The use of β blockers or hypoglycemic or diuretics drugs was not significantly different between subjects with normal STT and those with prolonged STT > 12 min. Although subjects taking antihypertensive drugs had an abnormal STT more frequently, when this was included in a multivariate analysis model there was no association with prolonged STT.

The individual risk of prolonged STT as a function of DM, HTN, and these illnesses together is shown in Table 2. HTN with or without DM was associated with prolonged STT. Prolonged STT was also seen in subjects with DM who were 40 to 59 years old (*P* = .041). Using logistic regression analysis adjusted for age, sex, and health, significant and independent associations showed the influence of age and diseases (but not sex) on prolonged STT (Table 3).

There were no significant differences in in vitro mucus clearability and mucus contact angle when comparing healthy subjects with those with DM or HTN and among age groups. Consistent with earlier work,[34] the mucus contact angle was inversely correlated with airflow mucus clearability, but only in subjects with DM or HTN ($r^2 = -0.368$ and *P* < .001).

## Discussion

We used the STT to assess nasal mucociliary clearance and found that 81% of healthy subjects had normal nasal mucociliary clearance. Aging and DM and/or HTN were independently associated with decreased nasal mucociliary clearance. Previously, we reported a significant decrease in nasal mucociliary clearance in acutely ill elderly subjects, and prolonged STT correlated with increased hospital length of stay.[8] Among the 16 subjects included in that study, 13 had DM or HTN. This raised the possibility that the results could have been affected by those chronic medical conditions, and this became the focus of the current study.

We hypothesized that DM and HTN may affect mucociliary clearance and mucus properties differently. DM could decrease sugar transport into cells and thus the efficiency of a system with high energy

Table 1—*Demographic, Clinical, and SF-36 Data Segregated by Age*

| | Healthy Group | | | Diabetes/Hypertension Group | | |
|---|---|---|---|---|---|---|
| Variables | < 40 y (n = 51) | 40-59 y (n = 18) | ≥ 60 y (n = 10) | < 40 y (n = 31) | 40-59 y (n = 45) | ≥ 60 y (n = 97) |
| BMI, kg/m² | 23 ± 3 | 26 ± 2 | 24 ± 3 | 25 ± 5 | 27 ± 4[a] | 28 ± 5[a] |
| Systolic BP, mm Hg | 115 ± 8 | 116 ± 6 | 118 ± 4 | 121 ± 17 | 130 ± 21[a,b] | 137 ± 17[a,b,c] |
| Diastolic BP, mm Hg | 76 ± 5 | 78 ± 4 | 73 ± 10 | 84 ± 13 | 87 ± 18[a,c] | 82 ± 12 |
| Oxygen saturation, % | 97 ± 1 | 97 ± 1 | 96 ± 2 | 97 ± 1 | 96 ± 1 | 96 ± 2 |
| Heart rate, bpm | 76 ± 9 | 71 ± 8 | 73 ± 15 | 78 ± 12 | 76 ± 12 | 73 ± 13 |
| Blood glucose level, mg/dL | 98 ± 10 | 99 ± 9 | 98 ± 6 | 187 ± 90 | 175 ± 98 | 156 ± 79 |
| SF-36 physical component summary | 52 ± 5 | 52 ± 5 | 48 ± 11 | 51 ± 8 | 46 ± 8 | 42 ± 10[a,d] |
| SF-36 mental component summary | 53 ± 7 | 51 ± 4 | 47 ± 14 | 47 ± 11 | 49 ± 11 | 50 ± 11 |

Data are presented as mean ± SD. Analysis done by two-way analysis of variance and post hoc Bonferroni correction. Bpm = beats per min; SF-36 = 36-Item Short Form Health Survey.
[a]$P < .01$ vs < 40 y healthy group.
[b]$P < .01$ vs 40-59 y healthy group.
[c]$P < .01$ vs ≥ 60 y healthy group.
[d]$P < .01$ vs < 40 y diabetes/hypertension group.

demand, such as ciliary beating. A study performed in 50 diabetic subjects, aged 16 to 85 years, measured significantly prolonged STT (mean values of 18.2 min) compared with young healthy control subjects.[35] This impairment in nasal mucociliary clearance was thought to be due to decreased water and electrolytes in the diabetic airway. In the present study, delayed nasal mucociliary clearance was more commonly measured in elderly subjects with DM and/or HTN. Subjects with DM or HTN who were under 40 had normal mean STT (10.1 min), similar to their healthy counterparts (9.6 min) and also similar to published data.[25-30] This may have been because younger subjects have more efficient homeostatic adaptive mechanisms to illness than do the elderly.[13,36]

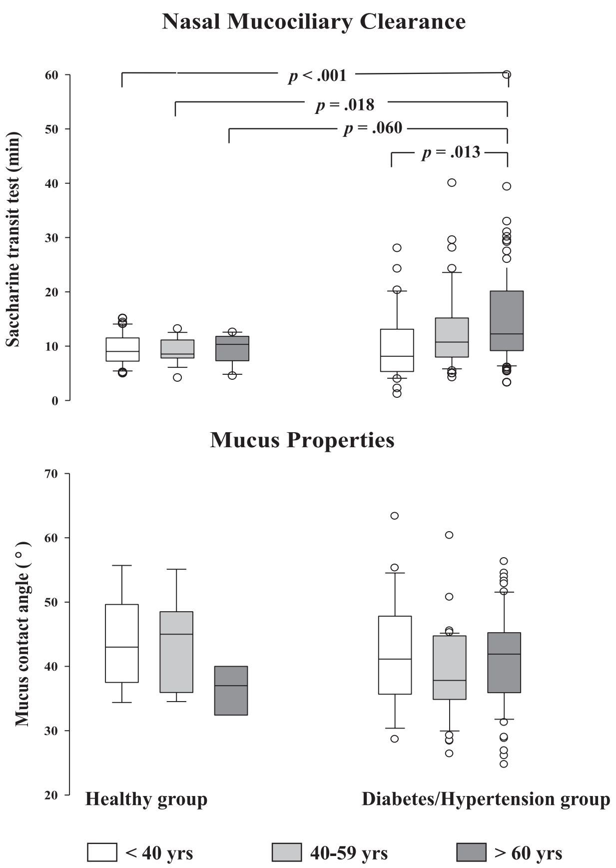


Figure 2. The saccharine transit test and mucus contact angle of healthy subjects and subjects with medical conditions by age (two-way analysis of variance with post hoc Bonferroni correction).

To our knowledge, there are no data on nasal mucociliary clearance and mucus properties in persons with HTN. Studies have suggested that some medications used to treat HTN may decrease mucociliary clearance in healthy humans. For example, β blockers may decrease ciliary beat frequency[37] and theoretically they could affect the autonomic regulation of mucus secretion. Diuretics may affect hydration of the mucus or periciliary layer.[25] The use of β blockers, diuretics, or antihypertensive drugs were not associated with prolonged STT in this study. However, it was difficult to study the effects of these medications independent of the underlying disease.

Some studies found similar mucociliary clearance[38-40] and ciliary beat frequency when comparing the elderly and young adults,[41] whereas other studies showed that aging is associated with slower mucociliary clearance in the upper and lower airways.[18-21,42,43] However, the health condition of the elderly subjects in most of these studies was not explicitly stated. We found that sex does not affect STT results but there is a 2% prolongation of STT for every 1 year increase in age. However, DM or HTN is associated with a 2.6-fold greater risk of prolonged STT.

In this study, the number of healthy elderly subjects without HTN or DM was small (n = 10) in part because of the subjects being identified in outpatient medical clinics. Nevertheless, the frequency of DM and HTN in the elderly subjects was similar to that reported in other reports.[8,20] We showed that aging is

**Table 2—*Individual Risk of Prolonged Nasal Mucociliary Clearance According to Chosen Variables in the Study Group (N = 252)***

| Variables | Total | No. Cases With Prolonged STT | Proportion of Prolonged STT, % | OR | 95% CI | *P* Value |
|---|---|---|---|---|---|---|
| Age | | | | | | |
| < 40 y | 82 | 19 | 23 | 1.00 | … | … |
| 40-59 y | 63 | 21 | 33 | 1.66 | 0.79-3.47 | .176 |
| ≥ 60 y | 107 | 54 | 50 | 3.38 | 1.74-6.57 | < .001 |
| Diabetes | | | | | | .040 |
| Yes | 121 | 53 | 44 | 1.71 | 1.01-2.88 | |
| No | 131 | 41 | 31 | … | … | |
| Hypertension | | | | | | < .001 |
| Yes | 136 | 65 | 48 | 2.75 | 1.58-4.78 | |
| No | 116 | 29 | 25 | … | … | |
| Diabetes and/or hypertension | | | | | | < .001 |
| Yes | 173 | 66 | 19 | 3.59 | 1.85-6.93 | |
| No | 79 | 15 | 46 | … | … | |

*P* values are given for $\chi^2$ analysis. STT = saccharin transit test.

associated with prolonged STT; however, the likelihood of decreased nasal mucociliary clearance was more strongly associated with DM and/or HTN in combination with aging.

Mucus properties could also have affected STT findings. Both contact angle and airflow clearance are sensitive to the conditions used for mucus preservation. It is important to note that all samples in this study were stored without oil preservative because this has been shown to invalidate rheology, contact angle, and clearance measurements. The contact angle results of the current study are similar to published results in young healthy subjects,[25] and the contact angle and airflow-dependent mucus clearability were similar between healthy subjects and those with DM or HTN, as well as among age groups. The well-reported correlation between mucus contact angle and airflow mucus clearability[44] was confirmed in this study as well. It is possible that the increased STT could be due to changes in ciliary beating but this was beyond the scope of this study.

There is evidence that the combination of advanced age and medical illness decreases quality of life.[45,46] DM and HTN can be associated with poor physical health and with disability.[47,48] We also found that the elderly subjects with illness reported lower perceived physical health than their healthy counterparts; however, there was no association of decreased quality of life with prolonged STT. All the healthy elderly subjects reported regular physical activities, such as walking or swimming at least twice a week, but this was true in only 37% of the elderly with HTN or DM; however, the difference was not significant, most likely because of the small number of healthy elderly subjects studied.

**Table 3—*Logistic Regression Model for Prolonged STT Adjusted by Age, Diabetes and/or Hypertension, and Sex (N = 252)***

| Factors | OR Crude | OR Adjusted | 95% CI | *P* Value |
|---|---|---|---|---|
| Age, y | 1.03 | 1.02 | 1.003-1.033 | .015 |
| Diabetes and/or hypertension, Y/N | 3.59 | 2.64 | 1.298-5.385 | .007 |
| Sex, female | 1.20 | 1.23 | 0.691-2.186 | .482 |

See Table 2 for expansion of abbreviations.

## Conclusions

In conclusion, aging and the chronic diseases DM and HTN are independently associated with decreased nasal mucociliary clearance. Although nasal mucociliary clearance differs from tracheobronchial clearance, delayed ciliary clearance may predispose elderly or chronically ill patients to respiratory infections.

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*Ms Proença de Oliveira-Maul:* contributed to the data collection, results analysis, and writing of the manuscript.
*Dr Barbosa de Carvalho:* contributed to the statistical analysis, discussion, results analysis, and writing of the manuscript.
*Dr Goto:* contributed to the data collection, results analysis, and writing of the manuscript.
*Ms Maia:* contributed to the data collection, results analysis, and writing of the manuscript.
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*Dr Perracini:* contributed to the results analysis and writing of the manuscript.
*Dr Jacob-Filho:* contributed to the results analysis and writing of the manuscript.
*Dr Saldiva:* contributed to the results analysis and writing of the manuscript.
*Dr Lorenzi-Filho:* contributed to the results analysis and writing of the manuscript.

*Dr Rubin:* contributed to the results analysis and writing of the manuscript.
*Dr Nakagawa:* contributed to the data collection, results analysis, and writing of the manuscript.

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