Non-Invasive Intracranial Pressure Estimation During Combined Exposure to CO_2 and Head-Down Tilt

Takuya Kurazumi; Yojiro Ogawa; Ryo Yanagida; Hiroshi Morisaki; Ken-ichi Iwasaki

BACKGROUND: Exposure to carbon dioxide (CO_2) and cephalad fluid shift are considered factors that affect intracranial pressure (ICP) during spaceflight. Increases in ICP were reported during cephalad fluid shift induced by head-down tilt (HDT), while little is known regarding the effect of additional CO_2 during HDT on ICP. Therefore, we tested the hypothesis that this combination increases ICP more than HDT alone.

METHODS: There were 15 healthy male volunteers who underwent 4 types of 10-min interventions consisting of Placebo/Supine (air and supine), CO_2/Supine (3% CO_2 and supine, CO_2 alone), Placebo/HDT (air and −10° HDT, HDT alone), and CO_2/HDT (3% CO_2 and −10° HDT, combination). Using arterial blood pressure (ABP) and cerebral blood flow velocity waveforms, ICP was estimated noninvasively before and during the four interventions. Two calculation methods were employed. One is based on the signal transformation from ABP to ICP with the intracranial component as a "black box" system (nICP_BB), and the other is based on the equation ICP = ABP − cerebral perfusion pressure, reflecting critical closing pressure (nICP_CrCP).

RESULTS: Both nICP_BB and nICP_CrCP significantly increased during Placebo/HDT and CO_2/HDT, although there was no statistically significant difference between the nICP indexes of these two interventions.

DISCUSSION: Increases in ICP were observed during both Placebo/HDT and CO_2/HDT. Contrary to our hypothesis, the combination of 3% CO_2 and −10° HDT did not increase ICP remarkably compared to −10° HDT alone. Therefore, the addition of 3% CO_2 is considered to have little effect on increasing ICP during cephalad fluid shift.

KEYWORDS: cephalad fluid shift, hypercapnia, intracranial pressure, non-invasive method, transcranial Doppler ultrasonography.

Kurazumi T, Ogawa Y, Yanagida R, Morisaki H, Iwasaki K. *Non-invasive intracranial pressure estimation during combined exposure to CO_2 and head-down tilt.* Aerosp Med Hum Perform. 2018; 89(4):365–370.

Onboard the International Space Station (ISS), astronauts face a risk of visual impairment and intracranial pressure (VIIP) syndrome.[14] Pathologies including optic disc edema, posterior globe flattening, optic nerve sheath distension, and choroidal fold are thought to be related to increases in intracranial pressure (ICP). However, the etiology of these changes remains unknown despite intensive investigations into this mission-critical medical problem that can affect astronauts during spaceflight.

The atmosphere inside the ISS contains concentrations (approximately 0.5%) of carbon dioxide (CO_2) that are over 10 times greater compared to the atmosphere on Earth.[10] Furthermore, astronauts face a risk of exposure to a high concentration of CO_2 due to the localization of CO_2 induced by the absence of natural air convection in microgravity.[11] An approximately 6-mmHg elevation in end-tidal CO_2 ($P_{ET}CO_2$) onboard the ISS was reported compared with sitting data on Earth.[6] In such an environment, there is a report that astronauts who experienced vision changes were exposed to higher concentration of CO_2 than those without vision changes.[25] Furthermore, as for cerebral circulation, we have demonstrated that the combination of mild hypercapnia (exposure to 3% CO_2; increases in $P_{ET}CO_2 \approx$ 6 mmHg) and cephalad fluid shift (−10° HDT) impaired dynamic cerebral autoregulation and increased cerebral blood flow (CBF).[9] Thus, investigation into the combined effect of CO_2 and cephalad fluid shift on ICP would also be important.

From the Nihon University School of Medicine, Tokyo, Japan.

This manuscript was received for review in October 2017. It was accepted for publication in January 2018.

Address correspondence to: Kenichi Iwasaki, M.D., Ph.D., Professor, Department of Social Medicine, Division of Hygiene, Nihon University School of Medicine, Tokyo, Japan; iwasaki.kenichi@nihon-u.ac.jp.

DOI: https://doi.org/10.3357/AMHP.5015.2018

Several studies using relatively direct measures have reported increases in ICP from a supine position to head-down tilt (HDT) as a ground-based analog for simulating microgravity.[5,12,17] One of these studies also investigated the addition of 0.7% CO_2 to the −6° HDT and indicated no effect on ICP.[12] From these previous studies, effects of HDT on ICP are apparent, but additional effects of elevated levels of inspired CO_2 are unclear. Thus, to date, the effect of the combination of mild hypercapnia (increases in $P_{ET}CO_2 \approx 6$ mmHg) and cephalad fluid shift on ICP remains unknown. To test our hypothesis that the combined exposure to 3% CO_2 and −10° HDT increases ICP more than −10° HDT alone, we estimated the ICP analyzing our previous research data from healthy subjects[9] using two noninvasive ICP calculation methods.[19,23]

METHODS

Subjects

The aim of the present study was to reanalyze the data of our previous research on the effect of mild hypercapnia and cephalad fluid shift on dynamic cerebral autoregulation[9] to estimate ICP. Participating in this study were 15 healthy male volunteers (ages 24 ± 3 yr; height 170 ± 5 cm; weight 69 ± 9 kg; mean ± SD). All subjects provided written, informed consent. The Ethics Committee of Nihon University School of Medicine approved the entire study protocol (No. 25-8-1), which was registered in the trial registry of the Japan University Hospital Medical Information Network (UMIN), ID: UMIN000017157.

Equipment

Continuous arterial blood pressure (ABP) in the radial artery was obtained noninvasively using tonometry (Jentow 7700; Colin, Aichi, Japan), and continuous CBF velocity (CBFV) in the middle cerebral artery (MCA) was obtained using transcranial Doppler (TCD) ultrasonography with a 2-MHz probe (Waki; Atys Medical, St. Genislaval, France). The details of the measurements were described in our previous report.[9]

Procedure

All subjects underwent four types of 10-min interventions that covered all possible combinations of exposure to a specific inhalational gas (either room air or a 3% CO_2 mixture consisting of 3% CO_2, 21% O_2, and 76% N_2) and position (either 0° supine or −10° HDT): exposure to air in the supine position (Placebo/Supine), exposure to 3% CO_2 in the supine position (CO_2/Supine, CO_2 alone), exposure to air in a −10° HDT position (Placebo/HDT, HDT alone), and exposure to 3% CO_2 in a −10° HDT position (CO_2/HDT, combination).

The waveforms for continuous ABP and CBFV were recorded at a sampling rate of 1 kHz, and the data were resampled at 100 Hz using Notocord-Hem 3.3 software (Notocord, Paris, France). The 6 min before intervention (breathing air in the supine position through a mask) and the latter 6 min of each 10-min intervention were extracted for analysis. ABP was corrected at the level of the MCA based on hydrostatic pressure.[9] Two noninvasive ICP calculations were performed every 10-s window, and the values of 36 windows were averaged.

The mathematical model for the noninvasive ICP calculation is based on the system analysis reflecting the physiology of the intracranial components, which is considered a "black box" (nICP_BB).[20] In this mathematical model, the rules for signal transformation from ABP to ICP are controlled by the relationship between ABP and CBF. First, based on the assumption that ABP is the input signal, the weight function between the ABP and ICP curves was computed. Second, the coefficients of the weight function between ABP and CBF were calculated by a transfer function every 10 s, which is used for hemodynamic characteristics. Finally, the relationship between ABP-ICP and ABP-CBF was calculated using multiple regression analysis, which provides the waveform of nICP_BB, which was assessed using a database of 145 neurosurgical patients.[19] This calculation was performed using plugin software "nICP Plugin" (Klinkum Chemnitz gGmbH, Chemnitz, Germany) for ICM+ version 8.1 (Cambridge Enterprise: http://www.neurosurg.cam.ac.uk/icmplus/, Cambridge, United Kingdom). These mathematical techniques in "nICP Plugin" consist of analytical methods described by Kasuga et al.[8, 20] They found that the major component of the intracranial pulse wave was about 1 to 20 Hz frequency, and demonstrated the greatest acceleration in transmission ABP-ICP occurred at about 10 to 15 Hz, as well as high correlation between estimated ICP and actual ICP at this frequency.[8] Therefore, the coherent relationship between ABP and CBFV throughout 1 to 15 Hz was calculated by transfer function analysis using DADiSP software (DSP Development Corporation, Cambridge, MA) to confirm the reliability of our collected data in the present study. The nICP_BB calculation was shown to correlate well with invasive ICP measurements in a large number of neurosurgical patients[1] and has been demonstrated to be the best estimator for the absolute ICP value among noninvasive ICP measurements using TCD.[2]

ICP was estimated using the equation: ICP = ABP − cerebral perfusion pressure (CPP). According to the concept of critical closing pressure (CrCP), CPP is related to cerebrovascular impedance, so this model can also estimate the ICP noninvasively (nICP_CrCP). Based on the physiological mechanism that CrCP is equal to the sum of ICP and vascular wall tension,[22] Varsos et al. established the following equation to estimate the CPP (eCPP):

$$\mathrm{eCPP} = \mathrm{ABP} \times \left[0.734 - \frac{0.266}{\sqrt{(CVR \times Ca \times HR \times 2\pi)^2 + 1}} \right] - 7.026$$

where CVR ($\mathrm{mmHg \cdot cm^{-1} \cdot s^{-1}}$) represents cerebral vascular resistance calculated as ABP divided by CBFV, Ca ($\mathrm{cm \cdot mmHg^{-1}}$) represents the compliance of the cerebral arterial bed calculated as the amplitude of the cerebral blood volume divided by the amplitude of ABP in 10-s windows, and HR is the heart rate ($\mathrm{beats \cdot s^{-1}}$).[23] Cerebral blood volume is estimated by integrating the difference between CBFV and the moving average of CBFV. Pulse rate was substituted for HR in

the present calculation. Then nICP_CrCP is obtained as the difference between ABP and eCPP (nICP_CrCP = ABP − eCPP). This calculation was performed using ICM+ version 8.1. The constant coefficients (0.734, 0.266, and 7.026) were derived from analysis of a database of 232 traumatic brain injury (TBI) cases.[23] In the present study, nICP_CrCP was considered to be a parameter that reflects the relative changes in ICP.

Statistical Analysis

Data are presented as the mean and SD. To strengthen the repeated-measures experimental design using the same 15 subjects, two-way repeated-measures of analyses of variance with periods (before and during intervention) × interventions (Placebo/Supine, CO_2/Supine, Placebo/HDT, and CO_2/HDT) were performed. The Student-Newman-Keuls method was used for multiple comparisons when significant differences were recognized. Values of $P < 0.05$ were considered significant. All analyses were performed using SigmaStat version 3.11 (Systat Software, Chicago, IL).

RESULTS

The results of the two noninvasive ICP calculations (nICP_BB and nICP_CrCP) are shown in **Table I**. For nICP_BB, there was a significant main effect of periods (before and during intervention) [$F(3,42) = 3.894$, $P = 0.015$, **Fig. 1A**]. The nICP_BB significantly increased during Placebo/HDT ($P = 0.002$) and CO_2/HDT ($P = 0.001$). There was also a significant main effect of interventions [$F(1,14) = 13.327$, $P = 0.003$, Fig. 1A]. Among the interventions, nICP_BB during CO_2/HDT was significantly higher than Placebo/Supine ($P = 0.019$) and CO_2/Supine ($P = 0.003$), but it did not show a significant difference compared to Placebo/HDT ($P = 0.117$). The interaction in nICP_BB was $P = 0.077$ [$F(3,42) = 2.451$]. The averages of coherence between ABP and CBFV in the range from 1 to 15 Hz were 0.61 ± 0.05 to 0.61 ± 0.05 (units, before to during Placebo/Supine), 0.62 ± 0.04 to 0.61 ± 0.03 (units, before to during CO_2/Supine), 0.60 ± 0.04 to 0.61 ± 0.06 (units, before to during Placebo/HDT), and 0.64 ± 0.06 to 0.63 ± 0.07 (units, before to during CO_2/HDT), respectively.

For nICP_CrCP, there was a significant main effect of periods (before and during intervention) [$F(3,42) = 267.55$, $P < 0.001$, **Fig. 1B**]. The nICP_CrCP significantly increased during Placebo/HDT ($P < 0.001$) and CO_2/HDT ($P < 0.001$). Furthermore, there was a significant main effect of interventions [$F(1,14) = 750.646$, $P < 0.001$, Fig. 1B]. Among the interventions, nICP_CrCP during Placebo/HDT and CO_2/HDT were significantly higher than Placebo/Supine ($P < 0.001$, respectively) and CO_2/Supine ($P < 0.001$, respectively). The statistical P-value between Placebo/HDT and CO_2/HDT in nICP_CrCP was $P = 0.05$. An interaction was recognized in nICP_CrCP [$F(3,42) = 421.533$, $P < 0.001$].

DISCUSSION

The present study had two major findings. First, increases in ICP were recognized during both Placebo/HDT and CO_2/HDT, estimated by two noninvasive ICP calculations (nICP_BB and nICP_CrCP). Second, there was no significant difference between Placebo/HDT and CO_2/HDT in nICP_BB. Thus, contrary to our hypothesis, the combination of exposure to 3% CO_2 (increases in $P_{ET}CO_2 \approx 6$ mmHg) and −10° HDT did not increase ICP significantly compared to −10° HDT alone. It is noteworthy that both noninvasive ICP calculations together detect the same pattern. Therefore, these results indicate that increased ICP was mainly induced by cephalad fluid shift with −10° HDT and that addition of 3% CO_2 had minimal effect on ICP during HDT.

The effect of cephalad fluid shifts produced by HDT as simulated microgravity on ICP has been investigated in healthy subjects,[5] ambulatory patients without indication for neurosurgical intervention,[17] and patients free of their diseases.[12] All of these studies showed increases in ICP during HDT using direct pressure measurements. Consistent with these previous studies, our noninvasive ICP calculations (nICP_BB and nICP_CrCP) also indicated increases in ICP during air inhalation in a −10° HDT position.

A previous study by Petersen et al. found increases in ICP of 4.9 mmHg during −10° HDT,[17] and Eklund et al. reported significant increases in ICP of 4.3 mmHg during −9° HDT.[5] Our present analysis, however, showed increases in nICP_BB of 1.9 mmHg. A relatively smaller change in nICP_BB compared to invasive measurements might result from the nICP_BB calculation underestimating the value compared to the measured value.[2] On the other hand, the nICP_CrCP showed relatively larger values in a −10° HDT. This index might reflect the increases in ABP directly due to the equation

Table I. The Means and SDs of nICP_BB and nICP_CrCP Before and During Intervention.

		PLACEBO/SUPINE	CO_2/SUPINE	PLACEBO/HDT	CO_2/HDT
nICP_BB (mmHg)	Before intervention	7.3 ± 2.4	5.8 ± 1.8	6.7 ± 3.0	8.1 ± 3.2
	During intervention	7.5 ± 2.2	6.7 ± 1.9	8.6 ± 3.5*	10.0 ± 2.2*,†
nICP_CrCP (mmHg)	Before intervention	13.3 ± 1.4	13.1 ± 1.3	13.4 ± 1.4	14.2 ± 1.1
	During intervention	13.7 ± 1.5	13.2 ± 1.5	28.2 ± 2.1*,†	29.2 ± 1.6*,†,‡

nICP_BB, noninvasive ICP calculation using mathematical model from the plugin software "nICP Plugin"; nICP_CrCP, noninvasive ICP calculation based on critical closing pressure.
* $P < 0.05$ compared to before intervention.
† $P < 0.05$ compared to Placebo/Supine and CO_2/Supine interventions.
‡ $P = 0.05$ compared to Placebo/HDT intervention.

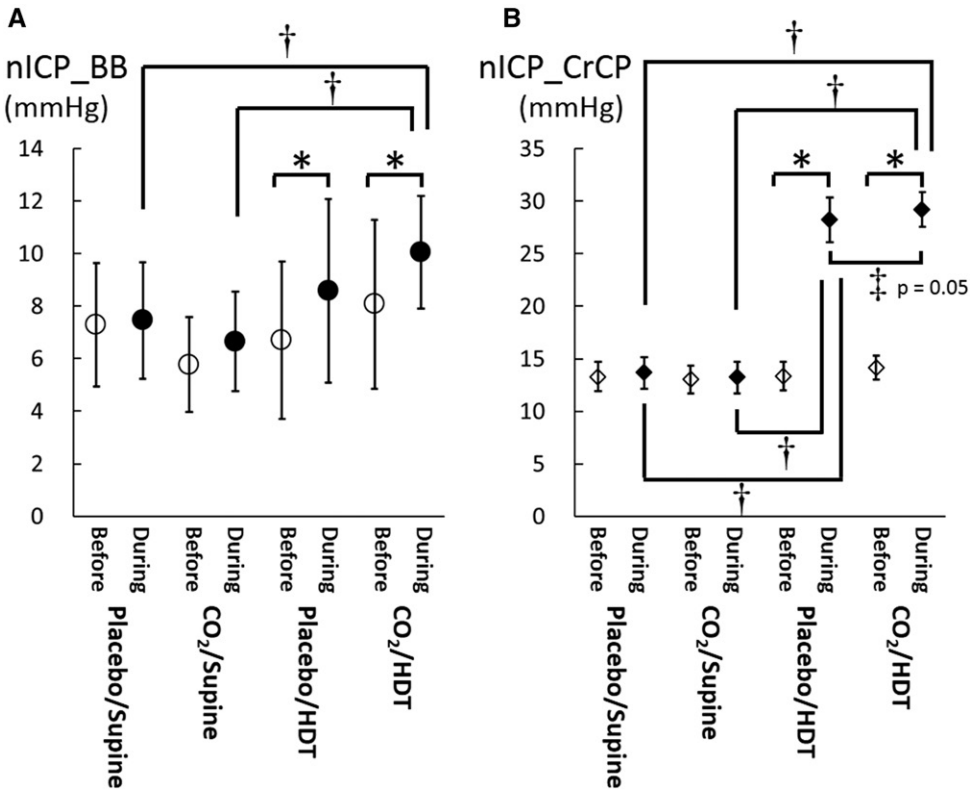

Fig. 1. The mean values of A) nICP_BB and B) nICP_CrCP before and during the interventions. Placebo/Supine, exposure to air in the supine position; CO_2/Supine, exposure to 3% CO_2 in the supine position; Placebo/HDT, exposure to air in a −10° HDT position; CO_2/HDT, exposure to 3% CO_2 in a −10° HDT position. BL, baseline; IV, intervention. Data shown as mean and SD. $^*P < 0.05$ compared to before intervention; $^\dagger P < 0.05$ compared to other interventions; $^\ddagger P = 0.05$ between the Placebo/HDT and CO_2/HDT interventions.

derived using data from TBI patients. As recommended by Cardim et al., integration of multiple methods would be appropriate to assess the change in ICP when a noninvasive ICP calculation is applied.[2]

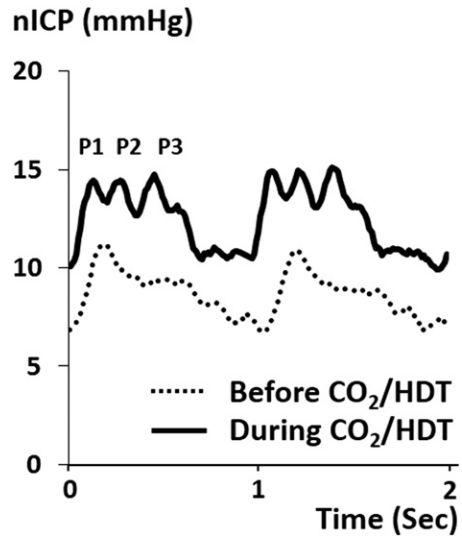

Fig. 2. The beat-to-beat ICP waveform of a representative subject before and during CO_2/HDT intervention, provided by nICP_BB calculation. The first fast peak of ICP associated with the fast propagation of the systole of arterial pressure is P1, the dicrotic notch occurring after the aortic valve closes is P2, and the tidal waves are P3.[18] Dotted line: before intervention; bold line: during intervention (CO_2/HDT).

Recently, Marshall-Goebel et al. found no effect of 1% CO_2 inhalation during −12° HDT on ICP compared to air inhalation during −12° HDT.[16] Other recent reports also showed that exposure to 0.5% CO_2 during −12° HDT[21] or exposure to 0.7% CO_2 during −6° HDT[12] was not associated with significant increases in ICP. These previous studies suggested that slight increases in CO_2 were not associated with clinical increases in ICP even during cephalad fluid shift. In the present study, even a 6-mmHg increase in $P_{ET}CO_2$ from exposure to 3% CO_2 did not show increases in ICP compared to normocapnia. Thus, these results suggest that up to an approximately 6-mmHg increase in $P_{ET}CO_2$ has little effect on increasing ICP even during cephalad fluid shift. However, evaluating results on scientific merits should be taken into account when the studies are tested with calculation of *P*-values.[13] The result of the nICP_CrCP during CO_2/HDT indicated slightly higher values than Placebo/HDT ($P = 0.05$). Therefore, if CO_2 concentration or number of subject is increased in the future study, it may lead to statistically remarkable significance.

The change in ICP is related to the regulation of cerebral circulation.[4] In subjects in the present study, we reported that dynamic cerebral autoregulation was impaired only by combination of 3% CO_2 and −10° HDT.[9] Similarly, Marshall-Goebel et al. reported alterations in cerebral hemodynamics caused by inhalation of 1% CO_2 during −12° HDT.[15] Thus, these two studies clearly demonstrated that the regulation of cerebral circulation is affected by the combined effect of hypercapnia and cephalad fluid shift. However, the combined effect on ICP was not recognized in both studies, unlike the regulation of cerebral circulation. There may be a difference in sensitivity between the changes in ICP and the regulation of cerebral circulation among healthy individuals.

Recently discovered visual impairments (VIIP syndrome) that take place during spaceflight are thought to be related to changes in ICP and/or intraocular pressure, cerebral circulation or other factors.[14,24] For applicability and ethical reasons, a noninvasive ICP estimation is more suitable for astronauts.

Noninvasive ICP calculation methods using TCD have been developed in clinical situations.[1] Especially nICP_BB calculation, including the regulation of cerebral circulation, has been established and correlates strongly with invasively measured

ICP.[2,19] Furthermore, this calculation method provides the beat-to-beat ICP waveform from the ABP waveform and CBFV waveform (**Fig. 2**). The shape of the ICP waveform consists of three components (P1, P2, and P3).[18] Under normal intracranial compliance, P2 and P3 are lower than P1. Contrarily, a reduced intracranial compliance manifests as elevations in P2 and P3. P2 and P3 are associated with the interaction between intracerebral blood volume and ICP.[3] These types of changes in the shape of the ICP waveform potentially reflect reduced intracranial compliance.[22] Thus, the change in shape of the ICP waveform may be a predictor for changes in the intracranial condition within the normal range of ICP. The noninvasive calculation using TCD is able to estimate the ICP, intracranial condition, and cerebral circulation, which is considered to be highly advantageous for application during spaceflight.

There are well-known limitations in studies measuring CBFV using TCD, i.e., the diameter of the MCA is assumed to be consistent, and the depth and the angle of the TCD are assumed to be repeatable. These limitations should be taken into account for the nICP_BB and nICP_CrCP calculations. The correction of ABP at the level of the MCA as an input signal to the nICP_BB and nICP_CrCP calculations instead of actual intracranial blood pressure should also be considered a limitation, although the correction of ABP with hydrostatic pressure has been considered to be appropriate for cerebral perfusion pressure.[7] Finally, the nICP_BB and nICP_CrCP calculations have been developed based on data from neurosurgical patients. Unfortunately, there is a paucity of data from healthy individuals. These noninvasive indices of ICP may not be accurate enough for the absolute values, but may be reasonably good for relative changes like the present results.

The present study estimated ICP during the combination of mild hypercapnia (exposure to 3% CO_2; increases in $P_{ET}CO_2 \approx$ 6 mmHg) and cephalad fluid shift (−10° HDT) using two noninvasive ICP calculation methods using TCD. Both noninvasive ICP calculations together indicated increased ICP during −10° HDT even with air inhalation or exposure to 3% CO_2. Contrary to our expectation, the combination of exposure to 3% CO_2 and −10° HDT did not increase ICP remarkably compared to −10° HDT alone. Therefore, there is little combined effect on changes in ICP.

ACKNOWLEDGMENTS

The authors would like to acknowledge Prof. Marek Czosnyka and Dr. Danilo Cardim for the technical assistance with the "ICM+" software, and Dr. Bernhard Schmidt for technical assistance with the "nICP Plugin" software.

This study was supported by JSPS KAKENHI Grant Number JP15H05939 for data analysis.

The authors have no conflicts of interest to declare.

T. Kurazumi designed the study, collected, analyzed and interpreted the data, and prepared the manuscript. Y. Ogawa designed the study, interpreted the data, and edited the manuscript. R. Yanagida designed the study, interpreted the data, and edited the manuscript. H. Morisaki designed the study, interpreted the data, and edited the manuscript. K. Iwasaki designed the study, analyzed and interpreted the data, and edited the manuscript.

Authors and affiliations: Takuya Kurazumi, M.D., Yojiro Ogawa, D.D.S., Ph.D., Ryo Yanagida, M.D., Ph.D., and Ken-ichi Iwasaki, M.D., Ph.D., Nihon University School of Medicine, Tokyo, Japan; and Takuya Kurazumi, M.D., and Hiroshi Morisaki, M.D., Ph.D., Keio University School of Medicine, Tokyo, Japan.

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