Research Article

Insights of Clinical and Medical Images

Efficacy Of Inhalation Instruction Using A New Real-Time Inspiratory Air Velocity Measuring Monitor

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Author Contributions:
Conceptualization, H.O. and S.H.; methodology, H.O. and S.H.; software, H.O. and S.H.; validation, H.O. and S.H.; formal analysis, H.O. and S.H.; investigation, S.K., O.F., and M.A.; resources, S.K., O.F., and M.A.; data curation, S.K., O.F., and M.A.; writing—original draft preparation, H.O. and S.H.; writing—review and editing, K.I. and T.O.; visualization, H.O. and S.H.; supervision, K.I. and T.O.; project administration, K.I. and T.O.; funding acquisition, K.I. and T.O. All authors have read and agreed to the published version of the manuscript.

Received Date: 10 July 2023
Accepted Date: 11 Aug 2023
Published Date: 21 Aug 2023

1. Abstract

An inhalation pattern is conventionally communicated to each patient by imaging verbal expression; as such, inhalation instruction may be ambiguous. A new inspiratory air-flow velocity measurement monitor (Tokico Inhalation Monitor, TIM) can visualize real-time inhalation patterns. We aimed to evaluate the usefulness of the TIM in the context of inhalation instruction. After verifying the responsiveness, accuracy, and reproducibility of the TIM, we evaluated the differences between the conventional verbal inhalation imaging and real-time instructions using the TIM. Six healthy subjects were measured individually after being given an oral image of the inhalation methods. We also compared the difference between the verbal images of traditional inhalation methods and the real-time inhalation instructions using the TIM. When the inhalation method was conveyed in words, the inhalation pattern differed depending on each subject's interpretation. By self-adjusting with repeated inhalation exercises with the TIM, total inhalation increased significantly to 1.90 ± 0.28 (L) ($p = 0.046$), compared to the 1.66 ± 0.39 (L) obtained during verbal imaging, while maintaining an adequate maximum inhalation flow rate of 62.2 ± 14.5 (L/min). In conclusion, using the TIM to perform inhalation exercises while drawing real-time inhalation patterns can increase the likelihood and efficacy of self-adjusted inhalation, and thus can make inhalation therapy more clinically useful.

2. Keywords:
Inhalation Instruction; Inhalation Pattern; Total Inhalation Volume; Maximum Inhalation Flow Rate

3. Introduction

Inhalation therapy is a pivotal treatment method for asthma and COPD, as indicated in major international guidelines. However, inhalation therapy is different from general oral treatment and is unusual for patients. The act of inhaling drugs is special and difficult for patients to perfectly understand and to adequately perform. The major reason for this is the existence of a dedicated device (inhalation device) being used at the time of inhalation. The biggest difference between inhaled drugs and oral drugs is not only the route of administration, but also the presence of an inhalation device that stores the inhaled drug inside and is used during inhalation. The main purpose of inhalation instruction is to maintain adherence, but inhalation therapy has two types of adherences: adherence to oral drugs and also to the inhalation devices used when inhaling [1]. Inhalation therapy is supported by these two adherence legs, and if one of the legs wobbles, the inhalation therapy itself will waver. Therefore, in inhalation therapy, the presence of an inhalation device is no less important than a drug.

The process of a series of drug inhalations consists of three phases from the perspective of the inhalation device. The first phase of the pre-inhalation stage is when the inhaled agent is set and prepared, the second phase is when the drug is inhaled, and the third occurs after inhaling the inhaled drug. When inhalation instruction is performed in daily clinical settings, various problems arise with inhalation devices in each phase. In the first phase for the pre-preparation of the inhaled drug, the patient is required to practice and become used to the precise operation of the inhalation device and the correct setting of the drug. In particular, for dry-powder-type inhalation medicine devices, the operation method for each device is unique and may differ greatly, so various erroneous operations

are likely to occur at the stage before the preparation of the set of inhaled drugs. A serious mishandling of an inhaled device can cause a loss of control and lead to a significant increase in emergency room visits and hospitalizations [2]. The mishandling of inhaled devices occurs more frequently, especially in the elderly [3], and this often leads to a failure in obtaining effective drug inhalation. The third phase includes gargling after inhalation, preparing for the next inhalation, keeping the device clean, and storing the device properly. The second phase of drug inhalation is the most fundamental and important phase in inhalation therapy. Patients are expected to inhale the drug at the proper rate and pattern of inhalation that best suits the individual inhalation device. However, despite the therapeutic importance the information concerning inhalation flow rate and inhalation pattern plays, as it is a pivotal role in inhalation therapy, the method of inhalation itself is almost always transmitted to the patient in the form of images of verbal expressions through oral or other means. Furthermore, each pharmaceutical manufacturer recommends the most suitable way to inhale its products in the form of images of each word, but the vocabulary is not unified and often ambiguous. For example, one dry powder inhalation device can use the words “inhale fast and deeply” to the patient, and another device uses the words “inhale fast and strongly” and “inhale as hard as possible”. As a result, the way the image of the word is received gives rise to various interpretations on the patient’s side, causing misunderstandings and self-indulgence. Even in the same patient, there is no standard for confirming which is the most suitable way to inhale, and this cannot be corrected. As such, there is always an instability in the treatment method, which does not lead to stable drug inhalation each time and adversely affects the effectiveness and adherence of inhalation therapy.

Respiratory function tests are performed as one of the grounds for the diagnosis and maintenance of treatment that occurs at the start of inhalation therapy in routine clinical practice. The indicators obtained by the respiratory function test are used to determine the severity and stage of the disease. They are also used to determine the therapeutic effect of the inhaled drug used, and all indices are obtained from the measurement of expiratory breath. However, it should not be forgotten that the inhaled drugs used in inhalation therapy are delivered into the lungs via inspiration rather than exhaled air. Therefore, a more important indicator in drug inhalation is the indicator of inspiration. In clinical practice, the maximum inspiratory flow velocity is often measured using the inspiratory air velocity InCheck® (manufactured by Clement Clark Int. Ltd., Essex, UK). The main purpose of its use is to confirm the patient’s potential to inhale at the maximum inspiratory air flow velocity that exceeds the minimum inspiratory speed required for each dry-powder-type inhalation device. Our previous studies showed that there are only a few patients that have a maximum inspiratory flow rate that does not reach the minimum inspiratory flow rate required by inhalation devices, and that there are almost no dry powder inhalation devices that cannot be used in terms of inspiratory air-flow velocity [4,5]. In the first place, reaching the maximum inspiratory flow velocity in an instant and then inhaling the drug is not the most effective way to inhale with the dry-powder-type inhalation device. On the other hand, aerosol-type inhalers are fundamentally different from dry-powder-type inhalers; however, in clinical practice, inhalation instruction has generally been to advise the patient to perform respiratory synchronization alone. There is no index that indicates how strong the inspiratory flow velocity is and how long it takes to inhale aerosol-type inhalers, and there is no standard for judging the quality of inhalation.

An important facet to any type of inhalation device is that, in order to effectively deliver the drug to the lungs, it is important to be able to inhale the air flow above the inspiratory air-flow velocity required by the device for a certain period of time. It is important to be able to capture and visualize in real time the “total amount of inspiratory air” obtained when each patient continues to inhale, while maintaining the inhalation within the effective inspiratory flow velocity value, for a certain period of time and how to utilize it for patient guidance. However, there is no instrument that can directly measure this index, and thus it has been left unexamined. Currently, the most evident blind spot in clinical practice with respect to this is the inability to provide inhalation guidance on the second phase of the drug inhalation process, i.e., the drug inhalation method itself. Ideally, individual inhalation guidance should be provided in which the current inhalation method used by the patient can easily, and with minimal invasiveness, be measured as many times as possible in a short period of time and, if it is not appropriate, the inhalation practice can also be repeated while judging the effect in a short time.

The Tokico Inhalation Monitor TM (TIM), originally developed by Tokico System Solutions Ltd., is a measuring monitor that can draw inhalation patterns in real time along with an actual measurement of inhalation flow rate and total inhalation volume; as such, it may be useful in clinical settings. Measurements with this monitor are simple, minimally invasive, and can be performed by the patient themselves. In this study, a mass flow sensor for gas measurement was used to construct a system of standard devices that can measure the intake state, such as inhalation flow velocity and total inhalation volume, and can verify the accuracy of the flow rate display of the TIM, as well as its responsiveness during measurement, its data reproducibility, and the visibility of the intake pattern display. We also evaluated the quality of the inhalation instruction method using the TIM in healthy subjects, which were only performed via the conventional image transmission of verbal expressions. We examined whether a more effective inhalation method could be achieved by practicing inhalation while measuring the inhalation pattern in real time with the TIM.

4. Materials and Methods

4.1. Device Configuration Of The TIM

An outline of the device configuration of the TIM is shown in Figure 1. In order to accurately measure the inhalation status, a thermal flowmeter (Siargo Ltd., California, US), which was already designed for ventilator and continuous positive airway pressure (CPAP) applications and is also used in clinical practice, was used as the flowmeter. A computer that displayed the status of inhalation on the screen and a flowmeter that enabled data collection using a microcomputer board were connected. The inhalation resistance value for each dry-powder-type inhalant device was

reproduced by attaching a dedicated adapter corresponding to each DPI used in InCheck®. As for the measurement method, the state in which an inhalation monitor was used is shown in Figure 1 by video URL: https://youtu.be/KSDQMe_BdW8 (accessed on 6 May 2023) and QR code. After the subject presses the start button of the TIM to which the disposable mouthpiece is connected and puts the device on standby, the measurement is started using the subject's own intake of air as a trigger; during this process, data are collected. The data are displayed on the screen as a change (sec) of the flow rate (L/min) over time.

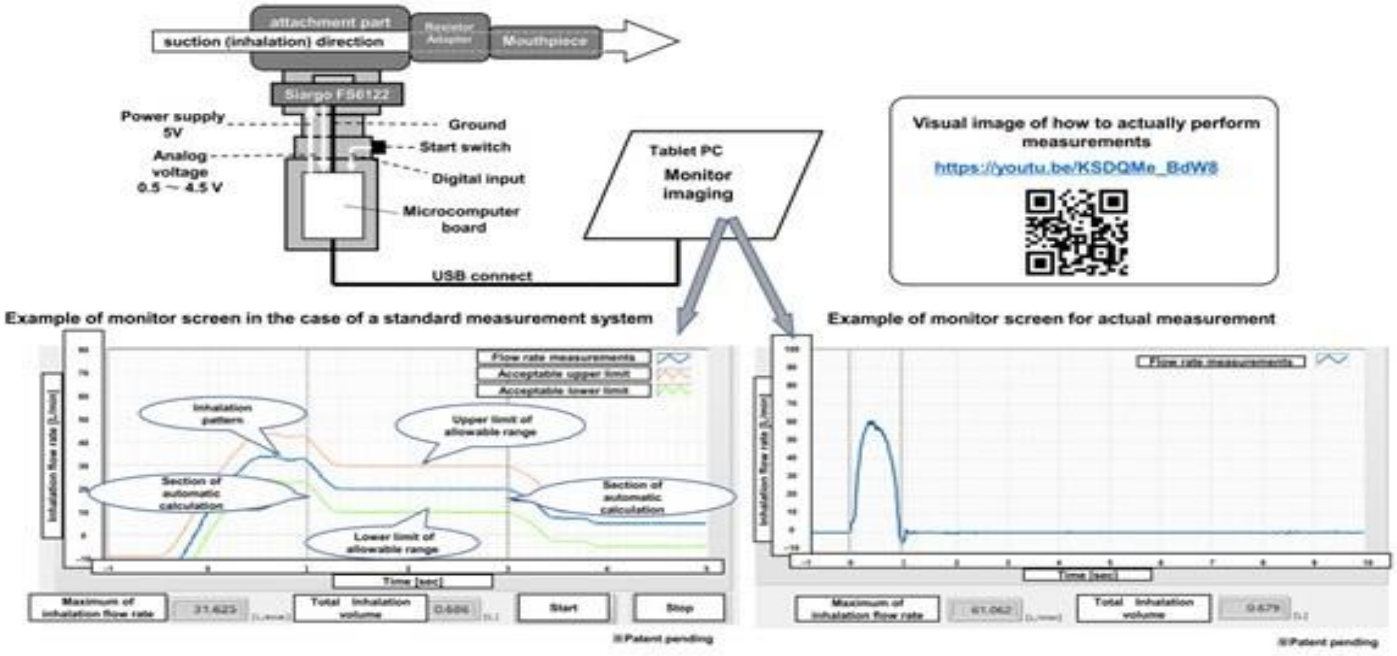


Figure 1: Equipment configuration of the Tokico Inhalation Monitor TM.

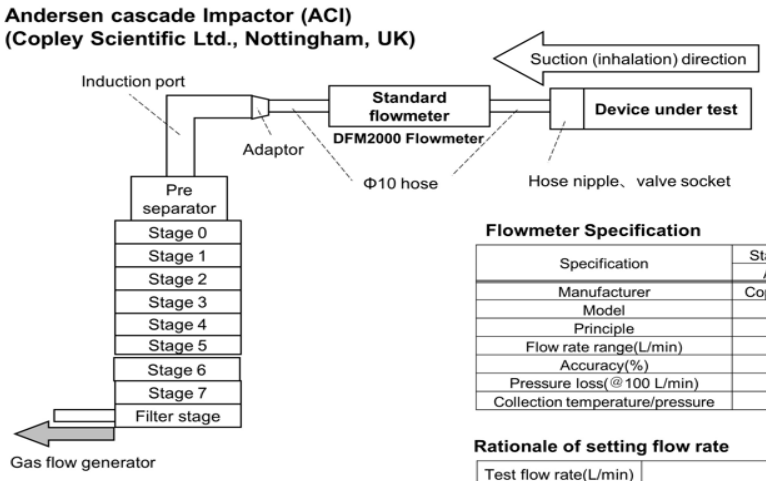
When used for inhalation guidance, it is also possible to determine whether the actual inhalation falls within that range by displaying the tolerance range before and after the inhalation pattern, which is an ideal reference, in advance. The maximum inhalation flow rate and total inhalation volume displayed at the bottom of Figure 1 are the measured values automatically calculated and displayed within the time area indicated between the dotted lines. By changing the dotted section to different time periods, it is possible to respond to various intake patterns.

4.2. Validation Of The TIM With A Standard Measurement System

Before using the TIM for measurement, we configured and verified the validity of the appropriate equipment configuration by configuring the standard measurement system. We verified and confirmed (1) the accuracy of the flow rate display, (2) responsiveness at the time of measurement, (3) data reproducibility, and (4) the visibility of the TIM's monitor screen.

Figure 2 shows an outline of the standard measurement system configured for this validation verification. In order to verify the accuracy of the flow rate display, we conducted the instrument difference test method from the Japanese industry standard "Calibration and vessel difference test of flowmeters for gases" [6]. In this method, the standard flowmeter, as a reference, was set to a constant flow value, measured simultaneously with the TIM—which is a flowmeter under test and connected in series3recorded the value, and confirmed the accuracy of the measured value of the flowmeter under test from the deviation of the numerical value. In addition, in order to confirm that this evaluation system was appropriate, the TF1000P flowmeter (Tokyo Keiso Co., Ltd., Tokyo, Japan), which has the same measurement principle, was compared and measured in the same manner. According to this standard, a temperature/pressure gauge was installed near the flowmeter to correct the flow rate. However, since each flowmeter itself is equipped with a temperature/pressure measurement function, in this study, the temperature was corrected according to the actual flow rate of the reference flowmeter based on the measured value of the flowmeter. In addition, the systems used for the evaluation of the inhalants, the Andersen Cascade Impactor (ACI) and DFM2000 flowmeter (Copley Scientific Ltd., Nottingham, UK), were used as flow generators and standard flowmeters for the evaluation system [7]. The configuration of the ACI consists of an induction port that is in the shape of the human throat, a pre-separator that traps coarse particles, and a stage for classifying the formulation into aerodynamic particle sizes according to the flow rate [8], which is also listed in the Japanese Pharmacopoeia Seventeenth Edition as a test and evaluation device for inhalants [9]. In order to accurately classify the formulation, measurement at a predetermined flow rate is required, but at the time the air flow was measured, and after confirming that the critical flow state was not affected by the pulsation of the pump, it is possible to adjust the intended flow rate, so a flow generation device was selected and used [10]. In addition, the DFM2000 flowmeter attached to the ACI can measure the flow rate with a higher accuracy using the same measurement principle as the flow rate under test at a designated time, and it is appropriate for

adoption as a standard flowmeter. The apparatus and each flowmeter were connected using hoses and joints of an appropriate diameter to ensure seal ability. Regarding the test flow rate, since the intake flow rate that is considered optimal for each device varies, the flow rate of five conditions was set as shown in Figure 2, based on the recommended values for each device.



Detail information concerning each ACI stage

Stage	Particle size (μm)	Corresponding to human part
0	9.0 ～ 10.0	-
1	5.8 ～ 9.0	-
2	4.7 ～ 5.8	Pharynx
3	3.3 ～ 4.7	Trachea, Primary bronchi
4	2.1 ～ 3.3	Secondary bronchi
5	1.1 ～ 2.1	Terminal bronchi
6	0.7 ～ 1.1	Alveoli
7	0.4 ～ 0.7	Alveoli
Filter stage	-	-

Flowmeter Specification

Specification	Standard flowmeter	Device under test	
	ACI attachment	Inhalation monitor	For comparison
Manufacturer	Copley Scientific Ltd.	Siargo Ltd.	Tokyo Keiso Co., Ltd.
Model	DFM2000	FS6122-50F200-5P40-TH1	TF1000P-101-P04
Principle	Thermal flow	←	←
Flow rate range(L/min)	0～200	-50～200	0～100
Accuracy(%)	±2%RD	±2.5+0.5%FS	±2.0%FS
Pressure loss(@100 L/min)	4.0 kPa	70 Pa	2.5 kPa
Collection temperature/pressure	- (actual flow)	20 ℃, 101.3 kPa	0 ℃, 101.3 kPa

※%RD (Reading error): Error to measured value.
※%FS (Full-scale error): Error to maximum value of measurement range.

Rationale of setting flow rate

Test flow rate(L/min)	Setting rationale
75	Values exceeding the inhalation flow rate required by many devices.
50	Values around the middle of the inhalation flow rate required by many devices.
30	Minimum required inhalation flow rate required by many devices.
20	Minimum required inhalation flow rate by some type of devices.
15	Values below the inhalation flow rate required by commercially available devices.

Figure 2: Configuration of a standard measurement system for validation of the Tokico Inhalation Monitor TM

For the measurement at each test flow rate—assuming the standard deviation when there is a preliminary confirmation, using the TIM, a confidence interval of 95%, and a tolerance of 0.4 L/min—10 measurements were performed, and the average value was adopted. Further, the calculation of the total amount of inhalation was obtained by a calculation of the accumulation of the flow rate being accurately measured. From the measured value results of the output from the TIM every 0.01 s, the time when the measured flow rate starts to rise when the valve is opened is set as the start point, and the time when the measured value reaches the set test flow rate is set as the end point. From the data measured in the examination of the accuracy of the flow rate display, the following parameters were set: (1) accuracy of the flow rate display, and (3) reproducibility was determined from the standard deviation of each test flow rate of 10 times and the shape of the intake pattern.

4.3. Examination Of The Usefulness Of The TIM In Healthy Subjects

After confirming the validity of the TIM, it was used in healthy subjects and its usefulness was examined. The subjects were 6 healthy subjects (1 in their 40s, 2 in their 50s, 2 in their 60s, and 1 in their 70s, with a mean age 59.7 ± 10.4 years, male-to-female ratio: 3/3). This study strictly adhered to ethical principles detailed in the Declaration of Helsinki (revised in 2013) and the "Ethical Guidelines for Human Life Science and Medical Research Guidance (established on 16 April 2021)", and was approved by the Ethical Review Committee (Clinical Research Tokyo Hospital Ethical Review Committee, first on 24 July 2014, revised on 24 March 2022, approval number: 14072400) when implementing it. The registration data were managed using the subject identification code in accordance with the Personal Information Protection Law. Participants were fully briefed on the content of the research trial and a written consent was provided of their free will.

4.3.1. Examination Item 1: Inhalation Pattern Based on Verbal Expression Image

Measuring by the TIM

The following five verbal expression patterns of inhalation were presented orally to the subjects, and what kind of inhalation patterns each subject showed in response to the instructions was measured using the TIM. The five verbal expression patterns of inhalation were A: "Inhale fast and deeply", B: "Inhale with your usual breathing power", C: "Inhale slowly and long", D: "Inhale as if sucking juice through a straw" and E: "Inhale longer to suppress peaks and breathe more air". The maximum inhalation flow (L/min) and total inhalation volume (L) were compared, which were automatically calculated by the monitor. The expression D: "Inhale as if sucking juice through a straw" is an oral expression that has often been customarily used in daily clinical settings mainly in the primary care field as a method of sucking dry-powder-type inhalants. At the time of measurement, in order to reproduce the difference in the inhalation resistance value of each dry-powder-type inhalation device, each following adapter, when using InCheck® Clement Clark Int. Ltd., Essex, UK), was attached and measured: AAD adapter (reflecting the resistance value when

inhaling the Discus®, GlaxoSmishKline Japan, Tokyo, Japan), T adapter (reflecting the resistance value when inhaling Turbuhaler®, AstraZeneca Japan, Osaka, Japan), and HH adapter (reflecting the resistance value at the time of inhalation of the Handyhaler®, Boehringer-Ingelheim Japan, Tokyo, Japan). The resistance value when the adapter was attached was expressed through AAD < T < HH, which increases in the order of HH [11].

4.3.2. Examination Item 2: Usefulness Of Real-Time Inhalation Guidance Using The TIM

We examined how the total inhalation volume changed when the examinee did not look at the TIM screen and when they were only given verbal instructions regarding the inhalation method. Then, we also examined how the total inhalation volume changed when the subjects themselves checked their own inhalation pattern in real time while watching the TIM screen, and when self-adjusting their inspiratory air flow rate and inhalation duration so that they inhaled in a more effective way. This examination item was compared by installing the AAD adapter with the lowest resistance value.

4.3.3. Statistical Analysis

The statistical significance level was set at 5%. Within-group comparisons were analysed as nonparametric data using the Wilcoxon rank sum test. Statistical analysis was performed using JMP®14.1.0 Windows version (SAS Institute Inc., Cary, NC, USA).

5. Results

5.1. Validation Data of the TIMs

The results of each are shown in the order of (1) accuracy of the flow rate display, (2) responsiveness at the time of measurement, (3) data reproducibility, and (4) monitor visibility.

1) As shown in the comparison between Table 1 and Table 2, the flow rate measured 10 times by the TIM had a small error compared with the standard flow meters and the other devices under test (manufactured by Copley Scientific Ltd. and Tokyo Keiso Co., Ltd., respectively). At the inhalation flow rate range of 15~75 L/min, the maximum reading error was observed at the time of measurement of 20 L/min, and the error was 5.2%;
2) In addition, as shown in Table 3, the response at the time of measurement was 0.32 s, on average, with the TIM, with the largest delay in the inhalation flow velocity being 50 L/min until the flow rate display and after the start of inhalation reached the true value

Table 1: Accuracy of indicated value and reproducibility of standard inhalation monitor (Tokyo Keiso Co., Ltd. Tokyo)

Standard flowmeter indicated value (L/min)	**Each indicated value of Device under test (L/min)**												
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Average	SD	Error (%RD)
75.00	76.0	76.1	76.0	76.0	76.2	75.7	76.0	76.0	76.1	76.2	76.0	0.2	1.4
50.00	51.1	51.0	51.2	51.0	50.9	51.2	50.9	50.9	51.2	51.0	51.1	0.1	2.1
30.00	30.3	30.2	30.2	30.0	29.9	29.9	30.0	29.9	30.0	30.0	30.0	0.2	0.1
20.00	20.0	19.5	19.6	19.5	19.6	19.8	19.6	19.8	19.5	19.5	19.7	0.1	–1.7
15.00	13.4	13.4	13.4	13.3	13.4	13.3	13.3	13.3	13.3	13.3	13.4	0.1	–10.9

Temperature 19.7 20.5 ℃ Humidity 19.0 20.9

Table 2: Accuracy of indicated value and reproducibility of Tokico Inhalation Monitor TM

Standard flowmeter indicated value (L/min)	**Each indicated value of Device under test (L/min)**												
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Average	SD	Error (%RD)
75.00	77.55	77.75	77.13	77.52	77.03	77.09	77.17	77.02	77.30	77.28	77.29	0.25	3.0
50.00	50.68	50.90	50.55	50.90	50.95	50.51	50.60	50.54	50.41	50.35	50.64	0.21	1.3
30.00	31.38	30.95	30.36	30.52	30.51	30.93	30.83	30.95	31.02	30.92	30.84	0.30	2.8
20.00	21.87	20.85	21.49	20.87	21.03	20.40	20.76	21.25	21.09	20.83	21.04	0.41	5.2
15.00	15.75	14.96	15.09	15.18	15.31	14.97	15.28	15.24	15.51	15.29	15.26	0.24	1.7

Temperature 18.3 20.4 ℃ Humidity 17.8 20.8

Table 3: Responsiveness to inhalation of Tokico Inhalation Monitor TM

Standard flowmeter indicated value (L/min)	Time to reach each indicated value (sec)											
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Average	SD
75.00	0.27	0.26	0.29	0.26	0.29	0.27	0.22	0.25	0.25	0.25	0.26	0.02
50.00	0.44	0.31	0.32	0.32	0.31	0.32	0.32	0.28	0.30	0.32	0.32	0.04
30.00	0.15	0.21	0.19	0.20	0.20	0.23	0.24	0.21	0.23	0.21	0.21	0.02
20.00	0.06	0.06	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.05	0.05	0.01
15.00	0.05	0.04	0.04	0.04	0.06	0.05	0.06	0.06	0.05	0.06	0.05	0.01

3) Data reproducibility is shown in Figure 3. Since the intake start operation was performed manually at the measurement start point, artificial variation was observed for each measurement, but there was no variation in the measurement start time by the device itself or in the sudden fluctuation of the flow rate after opening and closing the valve. Except for immediately after the start of inhalation and just before the end, the measured values within the 2~9 s area of the graph overlap almost all of the inspiratory air flow velocities of 15, 20, 30, 50, and 75 L/min. [4] As shown in Figure 1, the visibility of the monitor of the inhalation pattern display on the Tokiko Inhalation Monitor TM was sufficiently high. In addition, both the mechanical inhalation pattern in the standard measurement system and the inhalation pattern by the subject by an actual person could accurately reflect and display the different inhalation patterns. At the bottom of the TIM screen, the automatically calculated real-time maximum inhalation flow rate value (L/min) and total inhalation volume (L) are displayed separately, which is a useful index and can help with judging the effect immediately after inhalation.

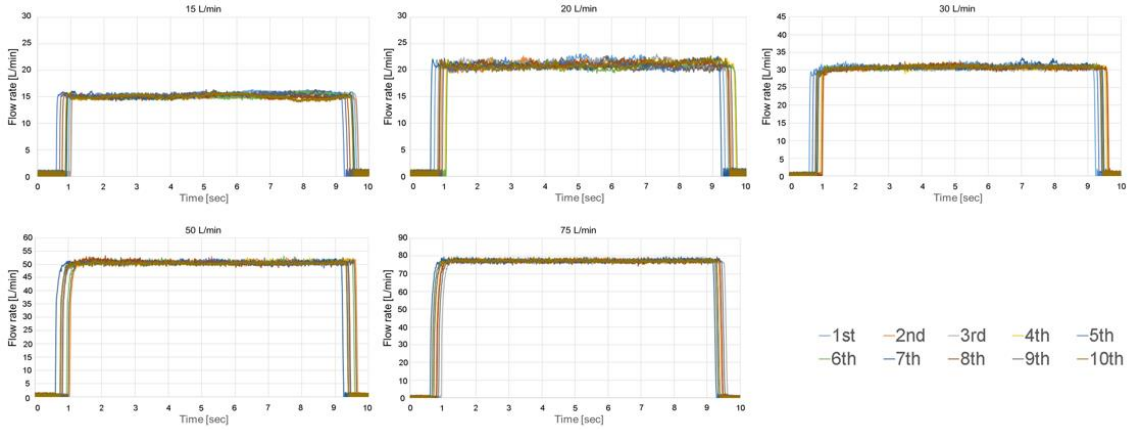


Figure 3: Evaluation of reproducibility of measurement by the Tokico Inhalation Monitor TM.

5.2. Usefulness of Real-Time Inhalation Guidance Using the TIM

Figure 4 shows the results of how each subject inhaled when they were transmitted the following five verbal expression patterns of inhalation: A:" Inhale fast and deeply", B: "Inhale with your usual breathing power", C: "Inhale slowly and long", D: "Inhale as if sucking juice through a straw", and E: "Inhale longer to suppress peaks and breathe more air". The maximum inhalation flow rate in Pattern A or C was a numerical value reflecting each verbal instruction, but when an adapter with a larger inhalation resistance value was installed, the maximum inhalation flow rate in Pattern A decreased, and the difference between the maximum inhalation flow rates in the A and C patterns was reduced. In Pattern B, the maximum inhalation flows varied greatly in individual patients and the total inhalation volume became the lowest in any case of AAD, T, or HH adapter.

In each dry-powder-type inhalation device, the value of the total inhalation volume should be expected as the largest value, usually when the patient is instructed to inhale as per Pattern A. Nevertheless, as per the result for Pattern C, the value of the total inhalation volume was the largest and most efficient inhalation. This indicated that Pattern C is the most effective inhalation method in any dry-powder-type device, which is particularly different to the conventional inhalation method (Pattern A) when using dry powder inhalation devices. In Pattern E, the variation of maximum inhalation flow rate becomes even smaller when the adapter has a high inspiratory resistance value depending on the subject. Nevertheless, the amounts of total inhalation volumes in Pattern E were relatively good in

all cases of the AAD, T, or HH adapters being used. However, the amounts of total inhalation volume tended to be better in Pattern C, rather than in Pattern E. This result was observed for any case of the AAD, T, or HH adapters being used.

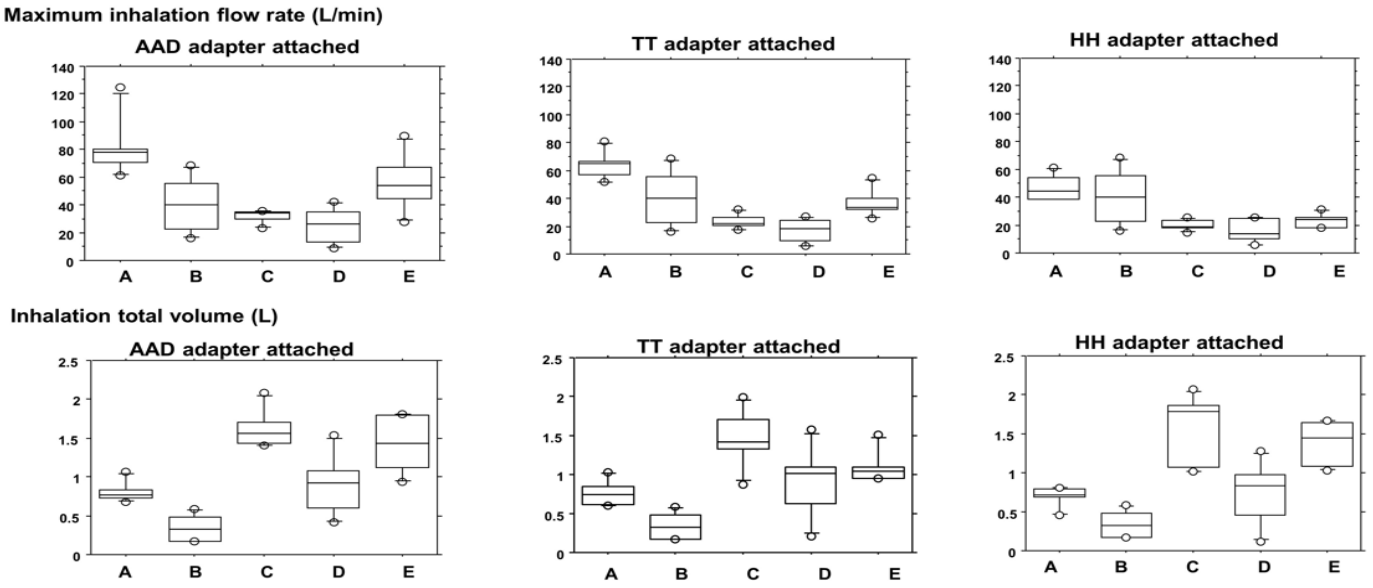


Figure 4: Comparisons of the maximum inhalation flow rate and total volume caused by the five different verbal expression patterns of inhalation. [five verbal expression patterns of inhalation] A: "Inhale fast and deeply", B: "Inhale with your usual breathing power", C: "Inhale slowly and long", D: "Inhale as if sucking juice through a straw", and E: "Inhale longer to suppress peaks and breathe more air".

In daily clinical settings, mainly in the primary care field in Japan, D: "Inhale as if sucking juice through a straw" has been conventionally used as a verbal expression used to efficiently inhale inhaled drugs. As shown in Figure 4, the amounts of maximum inhalation flow were the lowest among patterns A~E in any instance of AAD, T, or HH adapters being used, and the total inhalation volumes were not sufficiently good enough. (Figure 5) showed that the inhalation patterns varied greatly depending on the individual patient, and in the case of a device with a larger inhalation resistance, the total inhalation volume was significantly reduced, which resulted in efficient inhalation not being obtained.

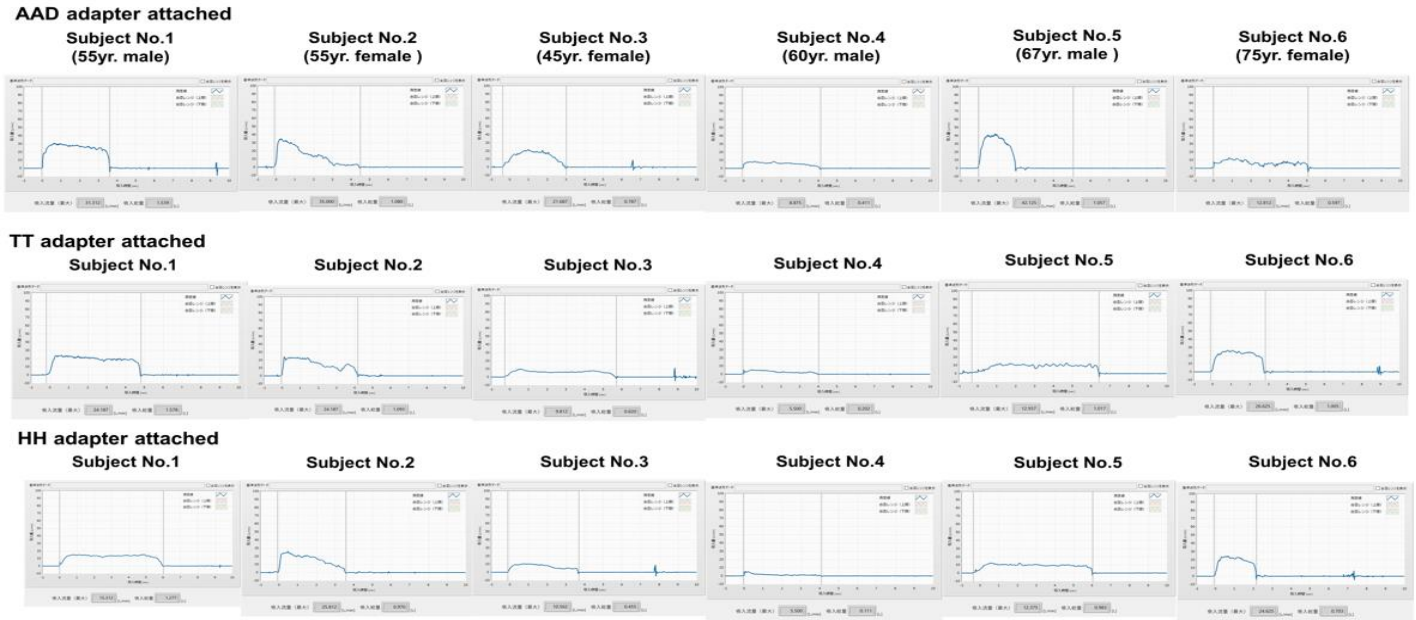


Figure 5: Comparison of inhalation patterns of individual subjects under the instruction "Inhale as if sucking juice through a straw".

(Figure 6) shows a comparison of the maximum inhalation flow rate and the total inhalation volume between the period when the oral transmission of verbal expression patterns took place with no watching of the monitor and when adjusting while watching the TIM to inhale as much air as possible. By inhaling while practicing the inhalation pattern in real time using the TIM, the maximum inhalation flow rate was 62.2 ± 14.5 (L/min) compared with 57.7 ± 14.8 (L/min) when instructed by verbal expression. The average value of the total inhalation volume significantly increased to 1.90 ± 0.28 (L) (n = 6, p = 0.046), compared to the 1.66 ± 0.39 (L) instructed by verbal expression, while maintaining almost the same level of maximum inhalation flow rate at 62.2 ± 14.5 (L/min).

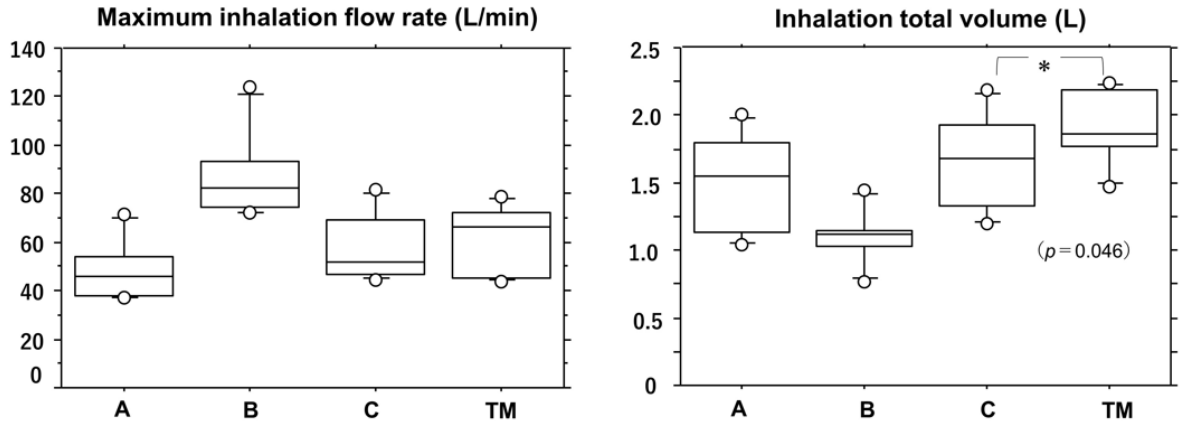


Figure 6: Comparison of maximum inspiratory air velocity value and total intake air volume between oral transmission using verbal expression patterns and the intake while using Tokico Inhalation Monitor TM (TIM) and looking at the monitor. Oral transmission of verbal expression patterns with no watching at the monitor A: "Inhale fast and deeply", B: "Inhale with greater vigor" and C: "Inhale longer to suppress peaks and breathe more air", and TM: "Adjust and inhale while watching the TIM monitor to inhale as much air as possible". Statistical significance: *p<0.05

6. Discussion

This study showed that the TIM is a useful measurement machine that was validated with standard measurement systems in terms of (1) accuracy of flow rate display and (2) data reproducibility. As shown in Table 1 and Table 2, the flow rate, which was measured 10 times by the TIM, showed almost no difference from the standard measurement system, and the accuracy of the flow rate display was also shown. The maximum error of the inhalation flow velocity in the TIM was 5.2%; however, assuming that this error can occur in the entire measurement flow range, when converted into a flow rate, the difference in absolute values was about 4 L/min or less. Furthermore, this error included variations in the actual flow rate due to changes in airflow conditions, which were due to pump pulsation, and the influence of measured values caused by pressure drops of two types of flowmeters, which were because the overall flow rate was high relative to the reference flowmeter. When the TIM was used during inhalation guidance, the error was so small that there was almost no problem, and the accuracy of the flow rate display of the device was maintained with sufficient accuracy. There was no problem with the TIM in the actual use conditions in the examination of readiness at the time of measurement. As shown in Table 3, the delay until the flow rate display reaches the true value after the start of inhalation in the TIM was about 0.3 s at most, and it can be said that the response at the time of measurement was sufficiently fast. In general, as the test flow rate increases, the time required for the airflow state to reach a stable flow rate and to reach a steady state tends to increase. In inhalation guidance, since inhalation is considered to be performed on a time scale of at least 1 s or more, the time to reach the actual flow rate indicated value of the inhalation monitor flowmeter was sufficiently short, and the patient's inhalation status was almost reflected in real time. Regarding the (3) reproducibility of the data, as shown in Figure 3, artificial variation was observed because the intake start operation was performed manually; furthermore, other than immediately after the start of inhalation and just before the end, the intake air flow velocity of 15, 20, 30, 50, and 75 L/min in any graph showed that almost all the measured values between the areas of 2~9 s overlapped, and it can be said that the measured values were sufficiently reproducible.

In most cases, in conventional inhalation instruction, the inhalation method specified by the inhalation device is shown to the patient in verbal expressions, and the patient inhales according to their self-interpretation of the content of the words transmitted by the image. The inhalation method with verbal expressions that has been transmitted to patients orally and by other means can be interpreted in various ways depending on how the patient receives it, causing ineffective inhalation and self-inhalation on a daily basis. Therefore, we used the TIM, which can accurately depict inhalation patterns, and examined what kind of inhalation patterns were shown by individual subjects receiving verbal expressions of how they inhaled. As shown in Figure 4, in the examination of the inhalation pattern of "Inhale as if sucking juice through a straw", which is conventionally widespread in Japan, varies significantly from subject to subject, and, in some cases, it may not be possible to say that it is a completely suitable inhalation method. This inhalation method is so widespread in Japan that it is currently introduced on the websites of various medical institutions,

but no evidence can be confirmed to support its effectiveness. The TIM is a machine that can visualize the inhalation patterns of individual patients in real time, including the maximum inhalation flow rate and the actual measured total inhalation volume. By effectively using the machine, measurements can be obtained easily and with minimal invasiveness many times in a short time, so as to approach the inhalation rate and inhalation pattern that is most suitable for the inhalation device being used by each patient. In addition, it can be practiced not only during patient inhalation guidance, but also by the patient themselves, and its clinical utility is also particularly high.

Inhalation therapy is the core treatment for asthma and COPD, but the inhaled drugs used are not cheap. From the perspective of health economics, cost performance is a very important factor. Today, the cost-effectiveness of drugs is becoming more important, especially for inhaled drugs, as there are relatively high unit costs [12]. If there is no confirmation that all inhaled drugs used in patients are effectively inhaled, then current inhalation therapy may not be cost-effective. If a doctor determines that the drug effect of the inhaler drug currently used is not sufficient in clinical practice, it may be easily changed to a more expensive inhaled drug, such as a combination drug with a higher therapeutic grade, and the cost-effectiveness will be even worse. In addition, as mentioned above, adherence to an inhalation device is important in inhalation therapy, but whether the inhalation method is effective can be unknown as the effectiveness is directly related to the adherence of the patient themselves. In recent years, cost-effectiveness from the viewpoint of adherence to inhaled drugs and drugs has also been examined [13]. From the patient's point of view, if the inhaled drug is not inhaled sufficiently effectively and the effect of the drug cannot be fully felt, it is likely to lead to a decrease in adherence. In particular, inhalation therapy is also a treatment that tends to reduce adherence [14]. Through this study, it was also suggested that the TIM may help to further increase inhalation efficiency and to increase the cost-effectiveness of inhalation therapy.

The limitations of this study are that the number of examinees were as small as six healthy subjects. The report did not examine actual asthma and COPD patients; furthermore, in order to use it as a medical measuring device in clinical settings, it was necessary to proceed with more accurate verification tests and safety tests, so there is still a long way to go before practical use. However, although this report is still in the research stage, it is significant in that it was an opportunity to focus on the inhalation act itself, which is an important second phase of the drug inhalation process and something that has not been fully examined thus far. We expect further research and development for the TIM, including joint development trials with the pharmaceutical manufacturers developing inhaled drugs, and toward the realization of actual clinical use in the future.

7. Acknowledgment

Institutional Review Board Statement:
The study was conducted in accordance with the ethical principles detailed in the Declaration of Helsinki (revised in 2013) and the "Ethical Guidelines for Human Life Science and Medical Research Guidance (established on 16 April 2021)". This study was approved also by the Ethical Review Committee (Clinical Research Tokyo Hospital Ethical Review Committee, first on 24 July 2014, revised on 24 March 2022, approval number: 14072400) when implementing it. The registration data was managed using the subject identification code in accordance with the Personal Information Protection Law.

Informed Consent Statement:
Informed consent was obtained from all subjects involved in the study. Participants were fully briefed on the content of the research trial and a written consent was provided of their own free will. Written informed consent was also obtained from the patients to publish this paper.

Data Availability Statement:
We have provided details in the paper regarding where data supporting reported results can be found.

Conflicts of Interest:
This research is a collaborative study with Tokico System Solutions Ltd. In conducting this research, the company lent us a new real-time inspiratory air velocity measuring monitor TIM with no charge. There are no other matters to be reported regarding the implementation of this study.

References

1. Ohbayashi H. Key points in effective inhaler technique training for asthma and COPD patients. Open J. Pharmacol. Pharmacother. 2020; 5: 27-29.
2. Melani A.S, Bonavia M, Cilenti, V, Cinti C, Lodi M, Martucci P and et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir. Med. 2011; 105: 930-938.
3. Barbara S, Kritikos V and Bosnic-Anticevich S. Inhaler technique: does age matter? A systematic review. Eur. Respir. Rev. 2017; 26: 170055.
4. Ohbayashi H, Hozawa S, Ohmichi, M, Oki K and Miyatake A. Current situation of asthma therapy by allergists in primary medical facilities in Japan. Allergol. Int. 2010; 59: 355-362.
5. Ohmichi M, Ohbayashi H, Oki K, Hozawa, S and Miyatake A. Examination of the inspiratory flow rates of COPD patients in Japanese medical facilities. Nihon Kokyuki Gakkai Zasshi. 2011; 49: 479-487.
6. Japanese Industrial Standards JIS B 7556; Calibration and Proving Test for Gas Flowmeter. Japanese Industrial Standards Committee: Tokyo, Japan, 2016; pp. 1-39.
7. Fontana M.C, Laureano J.V, Forgearini B, Santos J, Pohlmann A.R, Guterres S.S, de Arauj and B.V Beck. Spray-dried raloxifene submicron particles for pulmonary delivery: Development and in vivo pharmacokinetic evaluation in rats. Int. J. Pharm. 2020; 58: 119-429.
8. Nayak S, Ghugare P and Vaidhun B. Evaluation of Aerodynamic particle size distribution of drugs used in Inhalation therapy: A concise review. Int. J. Res. Granthaalayah 2020; 8: 264-271.

9. Ministry of Health, Labour and Welfare. 6.15 Aerodynamic Particle Size Measurement for Inhalations: Supplement 1 to The Japanese Pharmacopoeia Seventeenth Edition; Ministry of Health, Labour and Welfare: Tokyo, Japan, 2017; pp. 20-28.
10. Mohammed H, Roberts D, Copley M, Hammond M, Nichols S.C and Mitchell J.P. Effect of Sampling Volume on Dry Powder Inhaler (DPI)-Emitted Aerosol Aerodynamic Particle Size Distributions (APSDs) Measured by the Next-Generation Pharmaceutical Impactor (NGI) and the Andersen Eight-Stage Cascade Impactor (ACI). AAPS PharmSciTech. 2012, 13, 875-882.
11. Kondo T, Tanigaki T, Tazaki G, Watanabe H, Ishii H, Tsunoda T and Uruma T. The relationship between inspiratory pressure and flow through dry powder inhaler available in Japan. 2010; 59: 950-955.
12. Orlovic, M, Magni T, Lukyanov V, Guerra I and Madoni, A. Cost-effectiveness of single-inhaler extrafine beclometasone dipropionate/ formoterol fumarate/glycopyrronium in patients with uncontrolled asthma in England. Respir. Med. 2022; 201: 106-934.
13. Khaw S.M, Li. S.C and Tahir N.A.M. Measuring Medication Adherence in a Population-Based Asthma Administrative Pharmacy Database: A Systematic Review and Meta-Analysis. J. Asthma 2022;59: 697-711.
14. Cramer J.A, Bradley-Kennedy C and Scalera A. Treatment persistence and compliance with medications for chronic obstructivepulmonary disease. Can. Respir. J. 2007; 14: 25-29.