Semarak Current Biomedical Research Journal

Journal homepage:
https://semarakilmu.my/index.php/scbtrj/index
ISSN: 3030-5616

A Narrative Review of Capnography usage in Clinical Medicine

Bhuwaneswaran Vijayam[1,2,*], Sriwathi Angeline Hendricks[3], Ratnadeep Saha[4], Asila Shamirali Jiwa[5], Aneesa Maryam Basheer Ahmad[5], Kafuko Trevor Wamumbe[6]

[1] Department of Clinical Medicine, Newcastle University Medicine Malaysia (NUMed), 79200 Iskandar Puteri, Johor, Malaysia
[2] Regenerative Medicine Working Group, Newcastle University Medicine Malaysia (NUMed), 79200 Iskandar Puteri, Johor, Malaysia
[3] Independent Researcher, 81300, Skudai, Johor, Malaysia
[4] Department of Pre – Clinicals, Newcastle University Medicine Malaysia (NUMed), 79200 Iskandar Puteri, Johor, Malaysia
[5] NUMed Research Society, Newcastle University Medicine Malaysia (NUMed), 79200 Iskandar Puteri, Johor, Malaysia
[6] Super Protection Limited, Riaba, 240 Malabo, Equatorial Guinea, Guinea

ARTICLE INFO

Article history:
Received 29 March 2024
Received in revised form 9 May 2024
Accepted 20 May 2024
Available online 31 May 2024

Keywords:
Capnograph; capnometry; capnogram; capno; capnography; end-tidal carbon dioxide; carbon dioxide physiology

ABSTRACT

Capnography is the graphical study of carbon dioxide during expiration. Capnography has evolved and is more than merely a biomedical device that is used in the emergency department and intensive care unit (ICU). There are volume based and time-based capnographs. Although end tidal CO_2 ($EtCO_2$) is the most used parameter in clinical medicine, there are an abundance of other parameters from the capnometer. The capnographic parameters could originate from specific plot points of the time- or volume-based curves, the area under the curve or other mathematical and computationally transformed data of the CO_2. Although research of capnometry since its inception has focused on the respiratory aspects of the CO_2 signal with $EtCO_2$, newer parameters could be used to monitor, diagnose and prognose certain circulatory and metabolic disorders. In short, capnography is inevitably one of the important vital signs of modern medicine. As physiologically challenging conditions such as deep-sea diving and the now rampant space travel are becoming more common, there might be a need for familiarization with capnogram usage. In this narrative review, we go through the physiologic, mathematical, physics and clinical aspects of capnography.

1. Introduction

The Coronavirus disease 2019 (COVID-19) pandemic made us realize the importance of point-of-care devices and respiratory diagnostic tools for theranostic purposes [1,2]. In addition, parameters such as the pulse oximetry (SpO_2) which was widely used during the COVID-19 pandemic showed mixed results skewed towards being less reliable [3,4]. Besides that, the area of telemedicine had a growth spurt as the need for quarantine, isolation and minimal to non-contact diagnosis, supervision and surveillance were needed during the COVID-19 pandemic [5,6].

With all these factors, there were emergence and re-emergence of biomedical devices that served all these purposes. One of these was the capnometer. The capnometer measures the carbon

* *Corresponding author.*
E-mail address: bhuwaneswaran.vijayam@newcastle.edu.my

https://doi.org/10.37934/scbtrj.1.1.1839b

dioxide pressure signal in millimeter mercury (mmHg). When this is represented as a graph, the term capnography is used instead. In this narrative review, we go through the physiologic, mathematical, physics and clinical aspects of capnography. For brevity, capnography may be interchangeably referred to as ‘capno’ in this manuscript.

2. Carbon Dioxide Physiology in the Body

2.1 Breathing: A Physiological Process

Breathing is an indispensable physiological process which involves the exchange of gases between the lungs and the pulmonary capillary blood, which is also one of the most vital parameters of life. This process permits the body to remove CO_2 from the blood whereas the intake of oxygen (O_2) complements the need to support cellular respiration. Cessation of breathing often indicates an impending death and is one of the medico-legal criterions of death [7]. Breathing could be divided into two phases, namely the inspiratory and the expiratory phases. While breathing, the air needs to traverse a series of zones such as the upper conducting zone (nose, mouth, pharynx and larynx) followed by the lower conducting zone (trachea, bronchi and terminal bronchioles) and lastly to the respiratory zone (respiratory bronchioles, alveolar ducts and alveoli). During inspiration, air is sampled from the atmosphere to the terminal units of the lungs where O_2 is normally received into the bloodstream while CO_2 as biproduct of cellular metabolism of the body is deserted from the tissues to the blood and expelled into the atmosphere by expiration. It is also worth mentioning that the air residing in the respiratory tract does not partake in true gaseous exchange processes and is termed as anatomical dead space. This amounts to approximately 150 ml in healthy adults or nearly one third of the total tidal volume [8]. Physiological dead space refers to anatomical dead space and any other amount of dead space that fails to participate in gaseous exchange processes within the lungs despite being within the respiratory zone. Unutilized air residing within the respiratory zone usually represents negligible amount in healthy lungs and thus physiological dead space almost equals to anatomical dead space. This however is subjected to increase in various pathological instances when the diffusion capacity of the lungs (interstitial fibrosis) or the ventilation-perfusion ratio is compromised (pulmonary embolism and emphysema) [9–12].

2.2 Physiological Control to CO_2 Expiration

The lungs’ role in regulating CO_2 level in the blood is enormous. When we breathe in, inhaled oxygen is transported *via* the bloodstream to the tissues which is then utilized to yield energy and subsequently produce CO_2 as a waste product. This is carried through the blood back to lungs and removed through exhalation. Generally, the ventilatory control is sensed and exerted by a variety of receptors. Thoracic neural receptors residing in upper airways, trachea, lungs, chest wall and pulmonary vessels respond to lung volumes and various chemicals (histamines and prostaglandins) including irritant components (exogenous noxious agents) and chiefly responsible to the local chemical environment [13]. Activation signals to the respiratory center elicit alterations in breathing patterns primarily by increasing the respiratory rate and/or stimulating cough, bronchoconstriction and mucus production. Those with asthma, interstitial lung disease, pulmonary oedema, pneumonia and pulmonary embolism tend to show hyperventilation when these types of receptors are activated. Peripheral chemoreceptors while being in the carotid and aortic bodies are responsible to react if there is a change in arterial oxygen (PaO_2). However, they also equally enhance signaling to the brain in the event of hypercapnia and acidosis. Generally, discharge enhances when the partial pressure of arterial oxygen goes below 75 mmHg, and shows noticeable increase when it goes below 50-55 mmHg [14]. The combined impact of hypoxemia and hypercapnia always produce greater responses of the body than it does singly. Centrally located most pronounced chemoreceptors are mainly found close to the ventral surface of medulla and retrotrapezoid nucleus and play a significant role to act with urgency and powerfully to correct acid base irregularities by calibrating ventilation in response to a heightened PCO_2 situation. Owing to the lipophilic nature of CO_2, it crosses the blood brain barrier easily and thus is sensed rapidly by the brain to bring concomitant enhancement in ventilatory pattern and alteration in acidity. Pertinent to say that the influence of activation on centrally located chemoreceptors are much less while the acid base changes are metabolic in origin in contrast to respiratory type. The alveolar sacs are distal anatomical structures that are usually placed at the 20th to 23rd successful bifurcation of an ideal lung tissue [15]. Figure 1 shows the trends of O_2 and CO_2 values in mmHg in the atmospheric (1), inspired (2), alveolar (3), artery (4), vein (5) and expired air (7). Red arrows indicate the movement of respired air while blue arrows indicate expired air. The "METABOLISM" arrow shows the steady state of cellular respiration in which oxygenated RBCs are converted to deoxygenated RBCs.

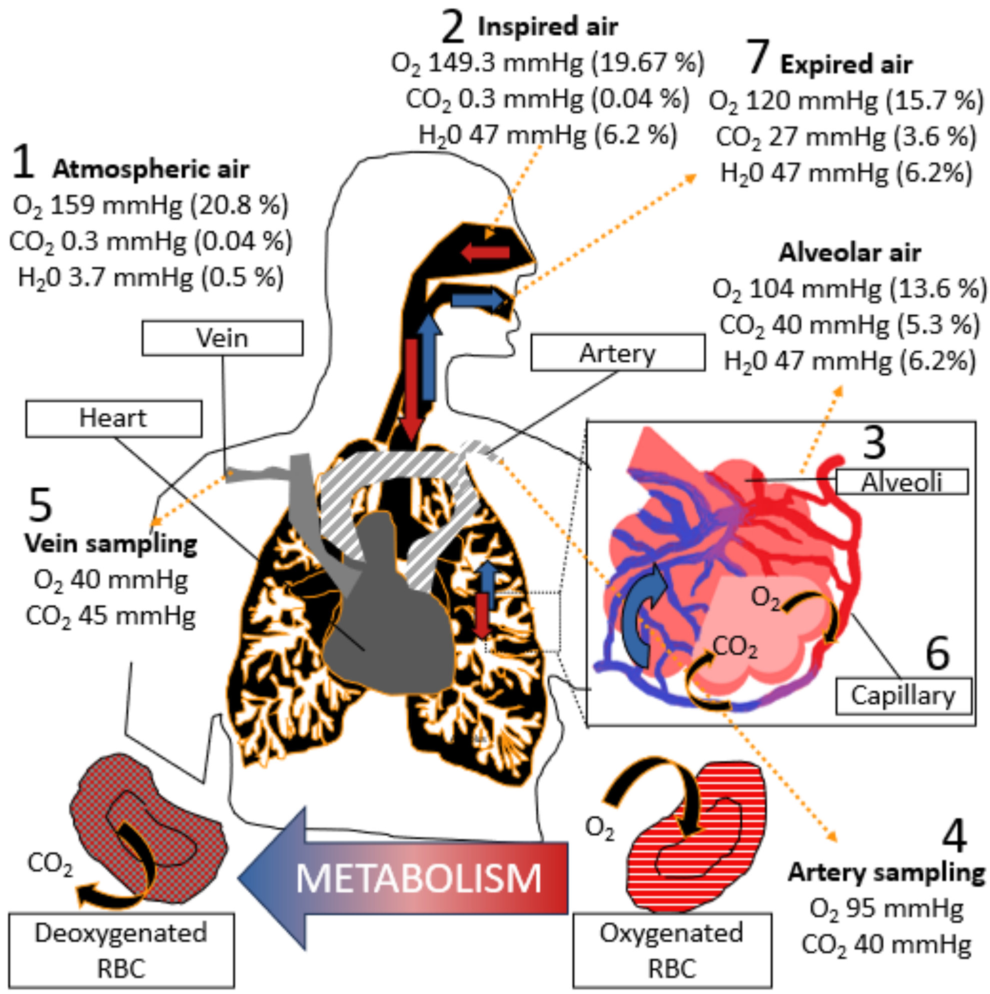

Fig. 1. Oxygen and carbon dioxide metabolism in the body

3. The Science of Capnography

3.1 Carbon Dioxide Fate: From One Red to Another

The content of carbon dioxide in the atmosphere is approximately 0.3 mmHg which makes up 0.04 % of the total gaseous content. Upon exhalation, the carbon dioxide increases to 27 mmHg. The content of carbon dioxide is higher in the alveolar region at 40 mmHg. The humidity of the inspired air is higher than the atmospheric air but remains unchanged in the expired and alveolar air [16,17]. The gaseous exchange in the alveoli could also be evaluated in the circulatory system *via* blood sampling of both the arteries and veins. Typically, the arterial blood would show a higher yield of oxygen and a lower carbon dioxide of 75 - 100 mmHg and 40 mmHg, respectively. The venous sample on the other hand has a lower oxygen and higher carbon dioxide concentration at 40 and 45 mmHg, respectively [18]. The arterial blood gas sampling remains the gold standard theranostic tool for cellular respiration in the clinical setting [19].

The gaseous exchange of carbon dioxide happens *via* diffusion through the deoxygenated red blood cells (RBCs) or better known as carbaminohemoglobin from the capillaries into the alveoli. CO_2 is transported from cells in the circulation towards the lungs in three forms which are the carbaminohemoglobin, bicarbonates (HCO_3^-) and the gaseous CO_2 form. Only 23 % of the CO_2 is transported *via* haemoglobin binding in contrast to HCO_3^- which owes to 70 % [20]. The CO_2 is 20 times more soluble than O_2 in the serum [20]. The carbaminoahemoglobin utilizes the reverse effect of Bohr or better known as the Heldane's effect for the transport of CO_2 into the alveoli [21,22]. In the capillaries of the alveoli, as the oxygen binds to the haemoglobin, the affinity of the haemoglobin towards the CO_2 is weakened owing to its diffusion from the capillaries to the alveoli. Other than that, the acidity of the haemoglobin is altered at this state to be more acidic thus converting the HCO_3^- to carbonic acid which readily cleaves into CO_2 and water. The CO_2 continuously diffuses through the alveoli [22]. Of note, other forms of metabolites such as carbon monoxide (CO) also undergo similar diffusion into the haemoglobin of the RBCs to form carboxyhaemoglobin.

As of late, non-dispersive infrared (NDIR) sensors are commonly used in medical devices. NDIR does not "disperse" or become scattered by substances between the light source and a detector [23]. NDIR sensors detect the CO_2 in a gaseous environment by its characteristic absorption and the vital components are an infrared (IR) source, a light tube, an interference filter (wavelength) and an infrared detector [24]. The exhaled CO_2 could be measured non-invasively through the manipulation of Lambert-Beer's Law (LBL) [25,26]. The equation of LBL is calculated from Eq. (1).

$$I = I_0 e^{-acl} \tag{1}$$

where, *I* represents the intensity of light striking the photodetector. I_0 represents the intensity of light of an empty sample chamber. *a* is absorption coefficient of CO_2. *c* is the concentration of CO_2 in mol/cm^3. l is the path length between the light source and the light detector. By using the LBL, the concentration of gas is typically calculated in IR spectroscopy [27]. From the same equation, radiation at wavelength 4.26 µm is associated with CO_2 concentration. Voltage corresponding to the amount of light which is absorbed by CO_2 contained in the respiratory gas is detected by a light-receiving element, thus detecting the CO_2.

Usually most small gaseous molecules exhibit a vibrational mode that also lies in the mid-infrared (MIR) range of 2.5 - 25 µm, and is also related with stretching, twisting, or bending their bonds. CO_2 gas has three vibrational modes: A symmetric stretch mode, a bending mode and an anti-symmetric stretch mode. The anti-symmetric stretch mode corresponds with the previously mentioned wavelength 4.26 µm in MIR and this is the most useful wavelength for measuring CO_2 because there are only few molecules which have a very little amount of significance of absorption at 4.26 µm range [23]. These concepts have also opened the manipulation of radiolabeled carbon dioxide presence, ratio, and recovery over time [28]. IR sensors are usually prioritized compared to other sensors such as chemical sensors which have a very low lifetime and need to be calibrated to maintain long term stability [29]. In summary, the CO_2 needs to be translocated from the 'red' blood cell to the infra-'red' sensor to display capnographic signals.

3.2 The Many Names of Capno

In 1860 John Tyndall inaugurally measured expired CO^2 by utilizing spectrum absorption with infrared technology [24-30]. This revolutionized the study of expiratory CO_2. "Capnometry' is the expirometric study of the CO_2 gas. It has been used for centuries and there are literatures as early as 1962 of its usage [31,32]. As it is conventionally known, the study of capnometry focuses mainly on usage of end-tidal carbon dioxide ($EtCO_2$). Although it is used interchangeably with "capnography", "capnometry" means only the measurement of CO_2 in respiratory gas without a continuous written record or waveform [33]. In an earlier paper in 1990, the author suggested that the measurement of $EtCO_2$ in numerical form is called a capnometry and when such occurrence is done in a continuous fashion whilst involving the analysis of the waveform, "capnography" is a better term [34]. The device which measures both capnometry and capnography is called a "capnometer". Meanwhile, colorimetric capnometry is often a victim of the misnomer capnography. The colorimetric approach does not yield any waves [35]. "Capnodynamic" is the combination of capno signals with positive end-expiratory pressure (PEEP)[36]. It could be used to detect cardiac output [37,38]. Figure 2 shows the summary of the differences between the discussed terms. Of note, although somewhat related, capnodynamic and quantification of radiolabeled carbon dioxide displacement would not be discussed as it is beyond the scope of this manuscript. These have been narrated extensively elsewhere [28,36,38].

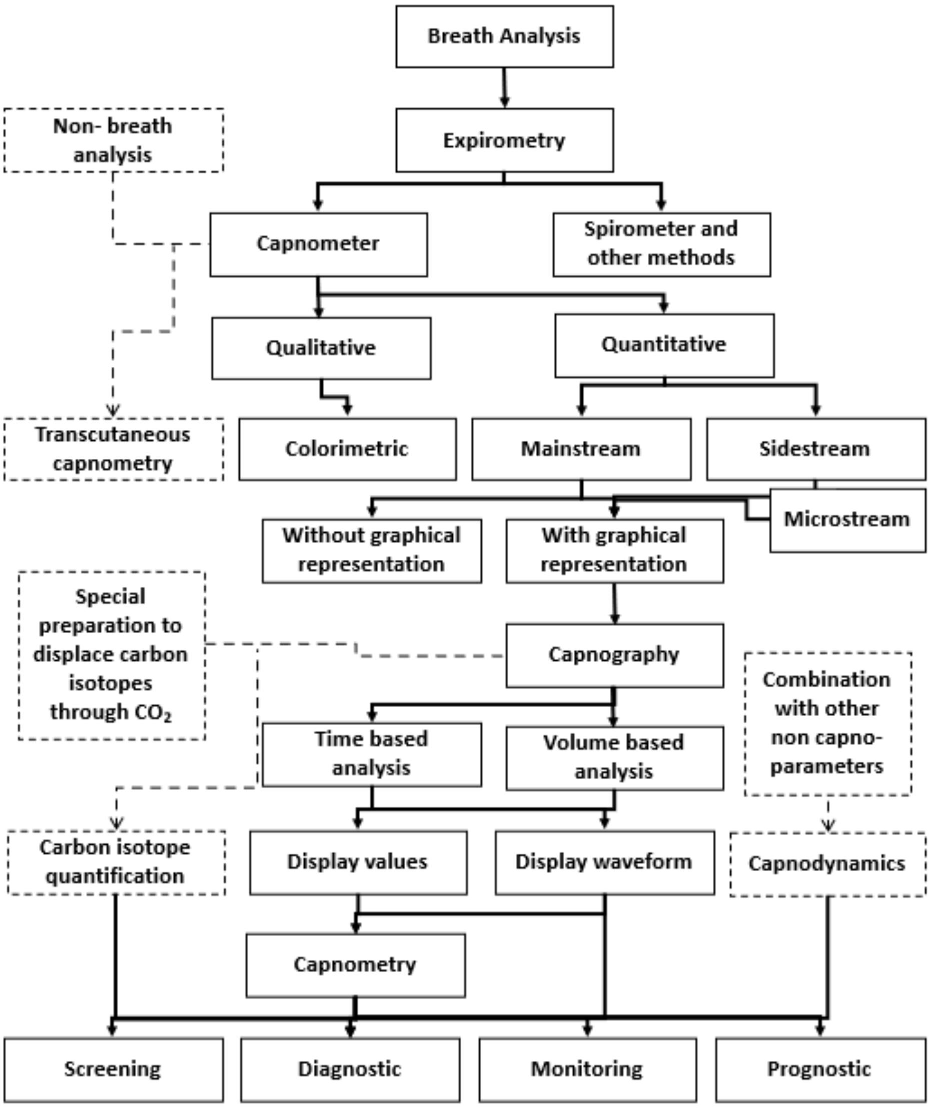

Fig. 2. The many names of capno: grams, graph, meter, metry and other

3.3 The Physics Behind Capnometry Stream, Waveform Signal, Flow, Volume and Time

Mainstream capnometers sensors are placed in between the proximal ET tube and the ventilatory circuit [39]. The mainstream capnometer could withstand flow range of the ventilator. Side stream capnometers use tubing connected to an airway adaptor and sampling line between the ETT and the breathing circuit to aspirate airway samples [39]. With side stream techniques, an IR sensor in a monitor could be placed which could be further away from the patient [39]. The flow rate for side stream varies between 150-200ml/L [40]. The side stream could be utilized in both intubated and non-intubated patients [41]. The low flow side stream or sometimes known as micro stream technology uses a flow rate of 50 ml/min [40,42]. Of note, there is a non-breath capnometer called the transcutaneous capnometer as depicted in Figure 2. This is discussed elsewhere as it is beyond the scope of this manuscript [43].

The time based capnograph is represented by CO_2 concentration on the y-axis and time on the x -axis as opposed to volume in the x-axis for volume based capnograph. The time based and volume based capno are sometimes abbreviated to TCap and VCap, respectively [44]. The TCap shows four phases which are phase 0, I, II and III. In contrast, the VCap does not have phase 0 as this represents inspiration [45]. Phase I represents free CO_2 in the anatomical and apparatus dead space [46]. Phase

II represents mixing of dead space and alveolar CO_2 depicting the S-shape [46]. Phase III represents the alveolar plateau and the maximum point which represents the $EtCO_2$ [46,47]. Additionally, in some articles, phase 0 is used interchangeably with phase IV [48]. Furthermore, SI, SII, SIII and SI are sometimes represented numerically as S1, S2, S3 and S4. Figures 3 and 4 show the TCap and VCap with the location of the phases. Phase I (depicted as magenta): Represents the CO_2-free gas from the airways (anatomical and apparatus dead space). Phase II (depicted as dark blue): Consists of a rapid S-shaped upswing on the tracing (due to mixing of dead space gas with alveolar gas). Phase III (depicted as orange): The alveolar plateau represents CO_2-rich gas from the alveoli. It almost always has a positive slope, indicating a rising PCO_2. Phase IV or 0 (depicted as cyan) represents the drop of CO_2 signal upon inspiration.

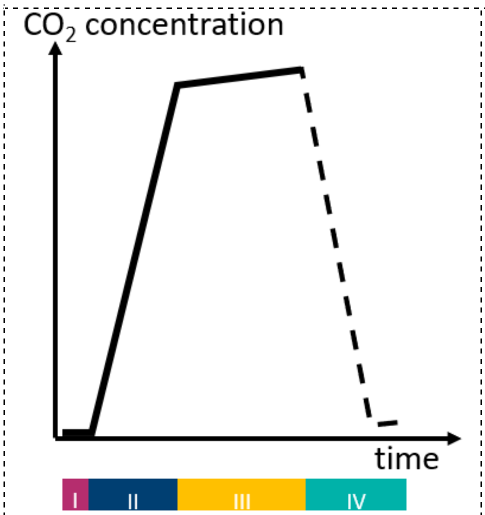

Fig. 3. Time-based capnography (TCap)

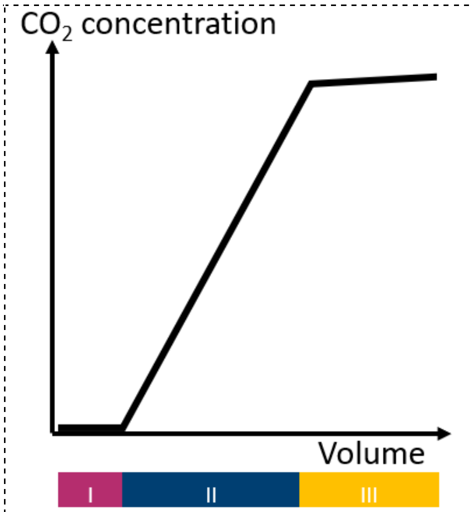

Fig. 4. Volume-based capnography (VCap)

Other major differences between the TCap and VCap includes the lack of dead space and dead space ratio calculation in TCap. On the other hand, the VCap lacks duration and temporal based capnometrics [49]. Both TCap and VCap could be manipulated to exert capnometric parameters such as frequency, efficiency, slopes, volume dead spaces and dead space ratios [49].

3.4 Capnometric Features

There are numerous of parameters that could be utilized ad manipulated in both TCap and VCap. We have divided these to at least seven proposed features. These includes carbon dioxide concentration points and coordinates, slopes, angles, areas and volumetric studies, transformation of capnometric data, combination of data with other non-capnometric parameter and morphological changes. These has been depicted in Figure 5.

3.4.1 Carbon dioxide concentration and time points and coordinates which signify certain clinical importance

An example of these phenomena is the $EtCO_2$ which is the peak of carbon dioxide concentration of at the alveolar level. Clinically, this also signifies the end of the expiration. This capnographic feature has the most usage in clinical practice. Other examples of points usage would be the Bohr's partial pressure of carbon dioxide ($PaCO_2$) based on the location of $EtCO_2$ [50]. Other than that, the determination of the beginning and end of a breath cycle which may be used to estimate the ratio and frequency of breathing.

3.4.2 Slopes

In 1994, You utilized the S1, S2 and its ratio to differentiate bronchospastic and non-bronchospastic patients [51]. This finding was later reiterated by Howe in which increment in both S1 and S2 was found in bronchospastic diseases [52] .Recent papers suggest the usage of slope II and slope III which slightly differs from the S1 and S2 as it uses the percentage of the whole breath duration rather than fixed coordinates in the S1 and S2 [53].

3.4.3 Angles

Few angles that have been in use are the take-off angle, alpha and beta angle. The alpha angle seems to be increased in bronchospastic diseases as reported by two separate papers by Howe and Nik Hisamuddin [52,54]. Other than that, congestive heart failure has shown different wave morphology when compared to normal cases [55]. Although no research on the morphological feature has been explained, we hypothesize that the beta angle and inspiration time would be increased in congestive heart failure cases.

3.4.4 Areas and volumetric studies

The volumes can measure at any point of both the inspiration and expiration phase. Other than that, the area under the curve (AUC) via the integration of a concentration wave over time can be used to estimate the tidal volume per breath ($VTCO_2Br$) at the alveoli per breath as done in previous studies by Tusman [56]. Meanwhile, the area above the curves (ABC) has been used by Bohr and Enghoff for dead volume studies as well as for the estimation of the arterial partial pressure of carbon dioxide $PaCO_2$ and mean expired carbon dioxide ($PeCO_2$) [57].

3.4.5 Functional transformation of wave data

A few other studies have optimized the functional transformation of data mathematically which uses the Hjorth parameter by squaring the mean variance of the S2 and S1 ratio [58,59]. Lukic *et al.,* [60] has used Root Mean Square (RMS) of CO_2 wave for the entire breath length for a better representation than mean value of the CO_2 obtained by standard equation [60]. A Linear Predictive Coding (LPC) was previously described by [58]. The same authors also proposed the usage of Power Spectral Density (PSD) *via* utilization of the frequency domain. The PSD was significant to differentiate bronchospastic conditions [58]. Of note, the VCap is more efficient and robust than the TCap in calculation of volume based capnometrics. Bothe the Bohr's ad Enghosff's spaces could be readily available with a VCap [61,62].

3.4.6 Combination of data with other non-capnometric parameter

Other than that, the transformation of the wave data may utilize the usage of other non-capnographic parameters. Capnodynamic which utilizes bot capnographic signals which combines CO2 signals from capno and PEEP is an example [37,38]. Other clinical significance of these combination of parameters for both time and volume based capno has been covered extensively elsewhere [48].

3.4.7 Morphological changes

Morphological change is the qualitative measure in evaluating capnography. Typically, the capnograph waveforms in TCap are quasiperiodic [63]. Among the common deviation from normal capnographic wave morphology includes absence of waves, changes in amplitude, duration and volume, cardiogenic oscillation, rebreathing patterns and the shark-fin pattern seen in bronchospasm. These are clearly depicted extensively elsewhere [64,65]. Figure 6 shows an example of the 'Crurare Cleft' pattern from our clinical experience in a patient who was not deeply sedated upon intubation. Meanwhile, as return of spontaneous circulation (ROSC) and pneumothorax's signal changes would be discussed in later part of this manuscript, apnea exerts morphological changes and CO_2 signal disappearance as reported by [66].

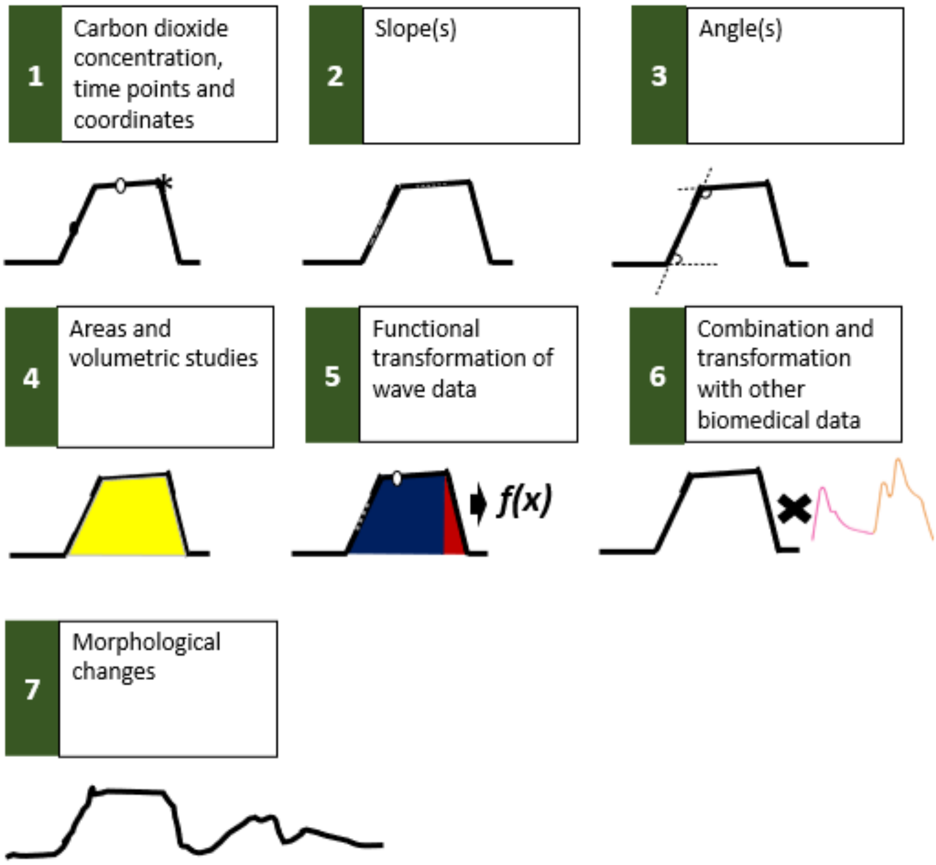

Fig. 5. Suggested feature classifications of capnometry

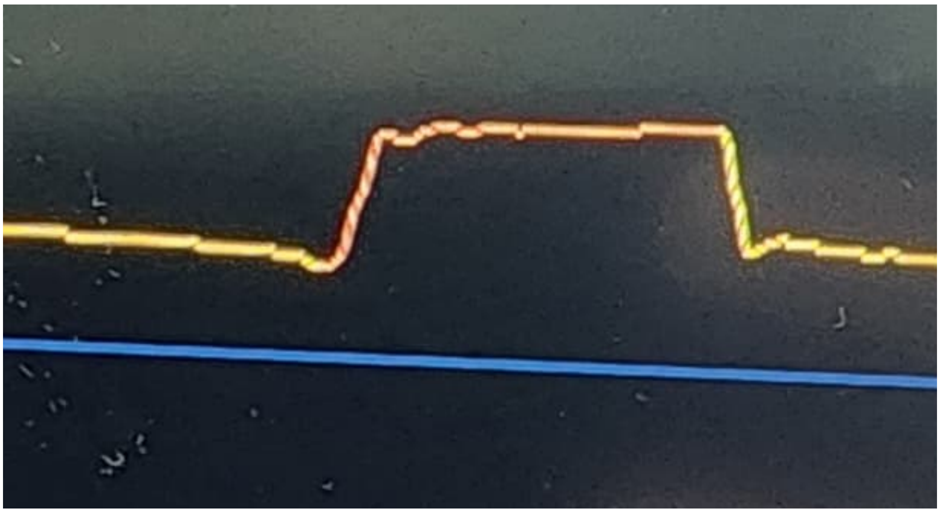

Fig. 6. Example of crurare cleft *(image courtesy of Dr Muhammad Aizuddin*)

Other clinical capnometric parameters for both TCap and VCap that has not been mentioned in this manuscript has covered elsewhere [48].

3.5 Capnograph Beyond $EtCO_2$

Most modern capnometers are still sole based on $EtCO_2$. Due to the limitations of current capnometers, the addition of custom signal processing or digitization methods are needed to yield capnometric parameters [67-70]. Figure 7 is an example of a signal derived from a TCap which shows several other non $EtCO_2$ parameters. S1, S2, S1-S2 slope, tidal volume per breath, alpha angle, Bohr's $PACO_2$ (represented as black diamond), $EtCO_2$ (represented as black star), inspiration plus expiration time and ratio. This could be programmed and computed as discussed by [67].

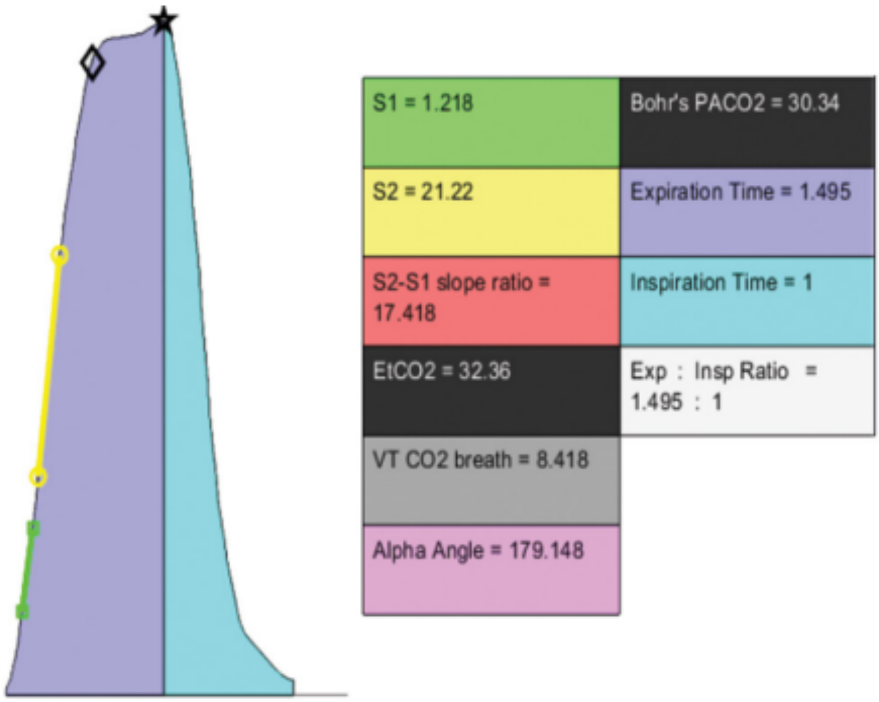

Fig. 7. Capnometric parameters in a digitized capnograph. Figure adapted and modified from [67]

3.6 Factors Affecting the Capnograph

Among the factors that may affect the capnograph signal originates from the subject or technical abnormalities. Factors such as rebreathing, depletion of CO_2 absorber, faulty valve, kinking, obstruction of the ET tube and extubation of the ET tube may all play a role in affecting the capnograph [43]. Meanwhile, subject conditions that leads to increase or decrease in CO_2 production, tachypnea or bradypnea and blood acidity levels are also the contributors for signal abnormalities [43].

4. Capnography and Clinical Medidcine

4.1 Conventional Usage of the Capnometer / Capnograph

Capnography has been used by anaesthetic and emergency clinicians to determine the placement of an endotracheal (ET) tube, to monitor the depth of sedation, to monitor respiratory acidosis and as a preventive measure to avoid carbon dioxide narcosis. Over the years, the usage has expanded towards the study of metabolism, circulation, lung perfusion and diffusion, quality of spontaneous respiration and the patency of airways, outside of its typical usage in the anaesthetic and emergency medicine field [71,72]. Additionally, ventilatory and device factors such as patency of the ET tube, state of connecting tubes, activity of CO_2 absorber and patient positioning on the operation table could also be monitored [72]. There are more parameters which are now recognized and being used at both bench side and bed beyond the sole usage of $EtCO_2$ in the capnometry alone. In 2017, Jaffe proposed that the capnographic analysis includes indices, slopes and angles, area, CO_2 waveform measures and statistics, frequency transformations, Hjorth parameters and areas [73].

Other interesting and selected capnometric parameters are shown in Table 1 and Figure 8. For easy reference, Table 1 has been sorted alphabetically according to the author's name.

Table 1
Selected clinical studies with distinct capnometric parameter(s)

No.	Referance and citation	Capno parameters involved	Clinical condition	Capnometer / Technology utilized
1	Abramo *et al.,* [74].	$EtCO_2$	Detection of respiratory failure and assess the requirement for intubation in actively seizing and post-ictal patients.	Sidestream capnometer (Pryon, Menomonee Falls, WI)
2	Alessandro *et al.,* [75].	$EtCO_2$	Chronic ketosis	Vmax Encore 29 System (Vmax) (Viasys Healthcare, Inc., Yorba Linda, CA).
3	Ansarin *et al.,* [76].	EtCO2	Mild and overt hypothyroid patients	(Microstream®; Oridion, Needham, MA)
4	Araujo-Preza *et al.,* [77].	$EtCO_2$	Feeding tube placement	The Easy-Cap (end-tidal CO_2 detector)
5	Baudendistel *et al.,* [78].	$EtCO_2$	Malignant hyperthermia	CO_2 Monitor (Datex)
6	Baudin *et al.,* [79].	$EtCO_2$, KPIV , $EtCO_2$ + KPIV, $EtCO_2$ + KPIV + FiO_2*	Estimation of arterial $PaCO_2$ in mechanically ventilated children	Capnostat 5 mainstream pediatric; Philips Healthcare, Markham, ON, Canada – volumetric Capnometry

7	Bradley *et al.,* [80].	CO_2 signal trace	Assist / anticipate difficult intubation with bougie	sidestream capnograph (FilterLine H Set Infant/ Neonate, Koninklijke Philips N.V, Amsterdam, Netherlands)
8	Brat *et al.,* [81].	$EtCO_2$, dead space volume to tidal volume ratio (VD/VT), VE/ VCO2 slope and VE/VCO2 ratio	Hyperventilation Syndrome	PowerCube-Ergo system (Ganshorn Medizin Electronic GmbH, Germany)
9	Brown *et al.,* [82].	Mean forced expiratory CO_2 values (1-6 seconds), slope of forced expiratory CO_2 curve		Capnostat® 5 mainstream CO2 sensor, Philips Respironics, Amsterdam, Netherlands).
10	Chebl *et al.,* [83].	$EtCO_2$	Diabetic Ketoacidosis	Philips intellivue MX700 Philips healthcare, Andover, MA).
11	Crures *et al.,* [84].	EtCO2 after a 3 second inspiratory hold (PLATCO2)	Approximation of arterial CO_2 pressure in acute respiratory distress syndrome in paediatrics	Sidestream technique via EngströmCarestation™ (GE Datex) and mainstream technique *via* Hamilton G5™ (Hamilton) MV
12	Diniz *et al.,* [85].	RR, Vd, VD/VT, $EtCO_2$, $PeCO_2$, VCO_2Br, slopes, inspiration and expiration time	Capnometric parameter and CT scan correlation in COPD	CO2SMO Plus (Dixtal/Novametrix Incorporation, Wallingford, CT, USA)
13	Dony *et al.,* [86].	$EtCO_2$	Hypocapnia under general anaesthesia and post operative 30 days mortality rate	sidestream CO_2 sampling (Perseus A500, Dräger, Lübeck, Germany
14	Eriksson *et al.*, [87].	SBT-CO_2, fDLate, PaCO2-EtCO2? VDPhys/VT	Diagnosis of pulmonary embolism	CO_2 analysis (CO_2 / Analyzer 130, Siemens Elema)
15	Fouzas *et al.,*	SII, SIII, VT, RR	Bronchopulmonary dysplasia	Unspecified CO_2 sensor
16	Howe *et al.,* [88].	$EtCO_2$, Phase II slope, Phase III slope	Asthma	Novametrix® capnometry
17	Jarenbäck *et al.,* [89].	Phase II, phase III, TLC, EFFi	Correlation of a new parameter (EFFi) with GOLD staging in COPD	Exhalyxer D: Mainstream capnograph
18	Kasuya *et al.,* [90].	$PaCO_2^*$ – $EtCO_2$ difference	Obese and non-obese subjects with and without sleep apnea	Cap-ONE mainstream capnometer system (Nihon Kohden) and Microcap sidestream capnometer
19	Kean *et al.,* [91].	A1, A2, AR slope 1, slope 2, Slope ratio, alpha angle Hjorth Parameters	Asthma diagnosis	Nihon Kohden Bedside Monitor BSM-2301K.
20	Kerklaan *et al.,* [92].	VCO_2	Energy expenditure in critically ill ventilated children	Servo-I® ventilator with the Capnostat-III sensor,

21	Lavillegrand *et al.,* [93].	Color change	Placement of feeding tube	Colorimetric capnometer
22	Lin *et al.,* [94].	$EtCO_2$, VD/VT	Surfactant therapy efficacy in preterm infants with low birth weight	Philips M2501A Mainstream Capnography
23	Luiz *et al.,* [95].	Tidal volume (TV), dead space (DS), DS/TV ratio, VCO_2, inspiratory and expiratory volume, Slopes	Respiratory function in Duchenne muscular dystrophy patients	CO_2SMO® Plus respiratory profile monitor (DX-8100 model, Novametrix Inc., CT, USA; Analysis Plus!® software).
24	Malarvilli *et al.,* [70].	A1-A6, S1-S6(All parameters are subsegments of the CO2 TCap signal)	ARDS diagnosis in COVID-19	Unnamed custom capnometer
25	Mieloszyk *et al.,* [55].	exhalation duration; $ETCO_2$; time spent at $ETCO_2$; and end-exhalation slope	Capnographic feature classification in COPD and congestive heart failure (CHF)	Capnostream 20(Oridion Medical, Needham, MA)
26	Moreira *et al.,* [96].	P(a-et) CO_2 gradient, $EtCO_2$, SIII III, fDlate	Pulmonary embolism monitoring / prognosis post thrombolysis	CO_2 SMO PLUS 8100 Dixtal/Novametrix™
27	Neumann *et al.,* [97].	KPIV	BPD	Ultrasonic flowmeter (Exhalyzer D, ECO MEDICS AG) which incorporates a mainstream carbon dioxide (CO_2) sensor (Philips Respironic)
28	Nitzan *et al.,* [98].	CO_2 signal detection	Minimally Invasive Surfactant Treatment (MIST) catheter placement in infants with respiratory distress	Commercial CO2 detector (Pedicap, Nellcor Colorado, USA)
29	Norweg *et al.,* [99].	$EtCO_2$	COPD therapeutic option	Information not provided
30	Peyton *et al.*, [100].	VCO_2 and $EtCO_2$	Cardiac output approximation in patient undergoing cardiac or liver surgeries	CO_2SMO+ inline infrared capnograph transducer and differential pressure pneumotachograph (Novametrix/Respironics USA)
31	Poon *et al.,* [101].	$EtCO_2$ for 3 minutes	ROSC in cardiac arrest patents	NellcorTM Microstream model N85 by Medtronic was
32	Ribeiro *et al.,* [102].	RR, inspiratory time (IT), expiratory time (ET), and the phase III slope normalized by expiratory volume (phase III slope/Ve).	Evaluation of airway obstruction in cystic fibrosis	CO_2SMO Plus Analyzer® (Respironics, Murrysville, PA, USA)
33	Shikama *et al.,* [103].	EtCO2, Slope III	Bronchospasm resolution	Information not provided

34	Singh *et al.*, [104].	$EtCO_2$, RR and Hjorth activity	Asthma diagnosis	Unnamed custom capnometer
35	Szakál *et al.*, [105].	EtCO2 and gastric artery PaCO2*	Estimation of splanchnic perfusion and a prognostic index also in critically ill neonates	Sidestream Microcap Handheld Capnograph.
36	Takaki *et al.*, [106].	EtCO2	Deep breathing exercise post abdominal surgery	Microstream, AG-400R, (Nihon-Kohden, Tokyo, Japan)
37	Talker *et al.*, [107].	α, β, γ, and δ angles; gradients and residuals derived from fitting curves to phases, absolute and short-term variability of pCO2; curvature; ratio of the expiratory to inspiratory phase ; area under the curve (AUC.	Real time diagnosis of COPD using machine learning	TidalSense's N-Tidal™ device
38	Tsai *et al.;* TBFL	Capno waveform	Pneumothorax	No information provided
39	Veronez *et al.*, [108].	RR, VCO_2, Phase 3 Slopes normalized for tidal volume (P3Slp/VE)	Lung disease evaluation in Cystic Fibrosis and Noncystic Fibrosis Bronchiectasis	$C0_2$SMOS Plus Analyser (Respironics, Murrisville, PA)
40	Vijayam *et al.*, [109].	EtCO2	Acute ketosis / Nutritional ketosis	Microstream Capnostream-20 capnometer (Covidien, Mansfield, MA),

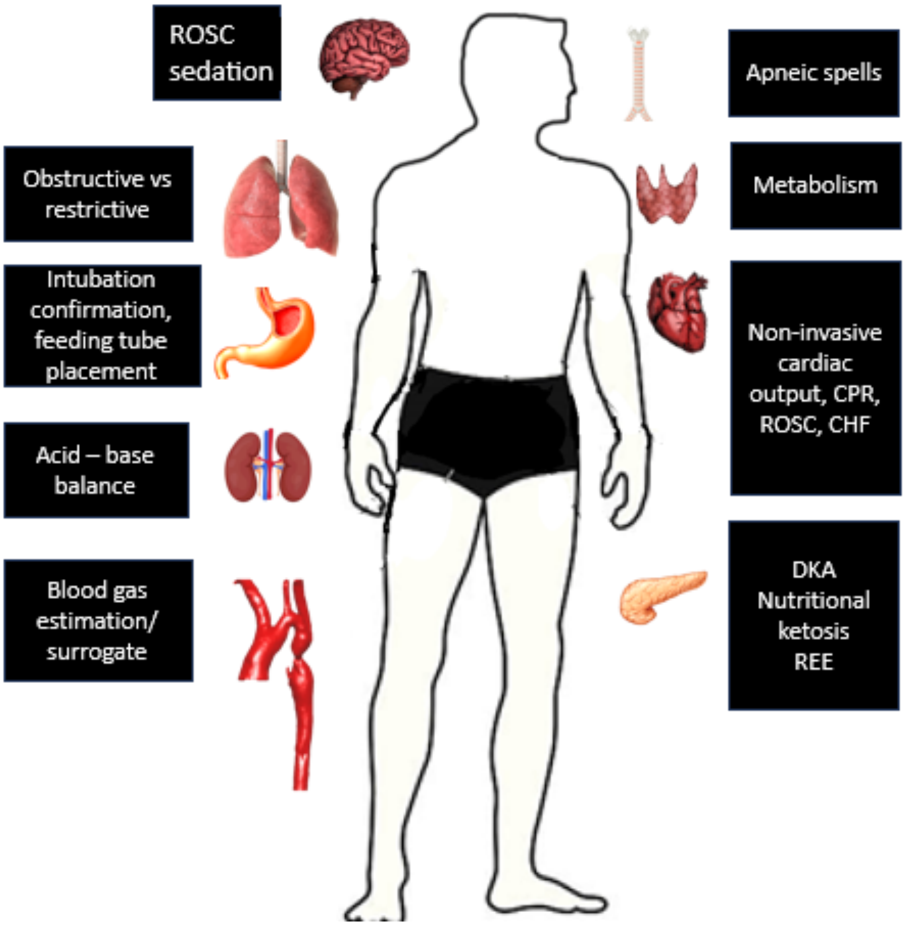

Fig. 8. The current possible clinical usages of capno

5. Current Limitations and Challenges in Capno Usage

5.1 Limitation of Capnography

There has been a vast capnometric usage of $EtCO_2$ despite the presence of capnograph in modern medicine. To add to this dilemma, the current medical exposure and training of capnometry is still low compared to colorimetric capnometer [110]. Other than that, most capnometers that are time based do not have flow as one other adjunct or complementary parameter. Likewise, the physiologic dead space parameters cannot be calculated when utilizing a time based capnometer. The mainstream and side stream devices serve different issues when it comes to dead space and inaccuracies when low tidal volumes are encountered [111].

From a clinical perspective, signals and waveform patterns of diseases such as pneumothorax and pleural effusion are not represented and have been depicted in any scientific article at the point of writing this manuscript.

5.2 Challenges in Capnography

Older devices show graphical representation with $EtCO_2$ value being the sole capnometric parameters. Additional measures must be taken to analyze other capnometric parameters. Signal processing of digital data or digitization of the capnographic images to analog prints may be applied [67–69].

6. Future Prospects of Capnography

6.1 Future Prospects

Among the prospects of capnograpy is the current expansion of usage. More diseases could be tested out as the capnography can be utilized for surveillance, monitoring diagnosis and prognosis. A particular are of interest would be metabolism as REE could be approximated by capnometric parameters [92]. Other than that, more integration and combination of non-capnometric parameters with the capnograph would yield better diagnostic sensitivity and specificity.

As for the device, there is a need for major improvement for the integration of capnographic parameters in newer devices. For older devices, signal processing or digitization of the capnograph could be a strategy to obtain the capnometric parameters as we have discussed earlier. Future devices should also focus on reducing device related errors such as rebreathing artefacts, motion artefacts and CO_2 signal leakage. Currently there are works in laser spectroscopy for high resolution capnography [112]. In addition, there are numerous techniques to obtain other capnometric parameters by manipulation both the VCap and TCap [113]. The utilization of artificial intelligence also increases the accuracy of capnometric parameters and may perhaps lead t discovery of newer ones [107].

There is a huge role of capnography is for space travel, monitoring in confined spaces underwater exploration and telemedicine to name a few [114–117]. These endless possibilities are depicted in Figure 9.

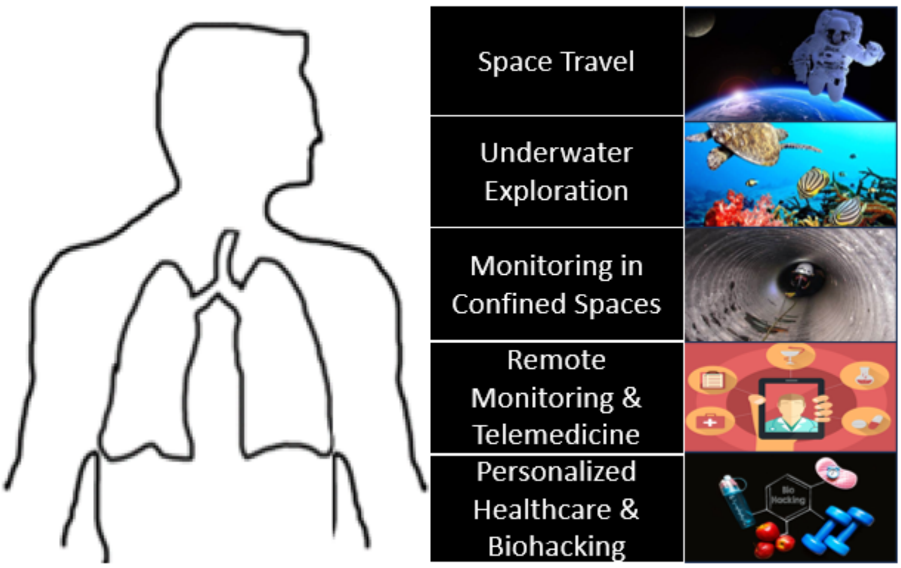

Fig. 9. Future possibilities and prospects of capnograph

7. Conclusions

The use of capnographs outside of the operating room, intensive care unit and emergency department is becoming more prominent. Capnographic data and interpretation are needed for both lung and non-lung diseases. As the age of telemedicine and remote human voyage and scavenging has already taken place, we believe that we have provided 'breathtaking' evidence that the capnography is a deserving candidate for the sixth vital sign in humanity.

Acknowledgement
This research was not funded by any grant.

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