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Clinical significance and various role of Perfusion Index in the disease management – A review

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ABSTRACT
In the fields of anaesthesia, perioperative care, and critical care, photoplethysmography (PPG) has been widely utilised for pulse oximetry monitoring. Certain PPG signal components, however, have been used for different objectives, such as non-invasive hemodynamic monitoring. The ratio of pulsatile to nonpulsatile light absorbance or reflectance of the PPG signal is represented by the perfusion index (PI), which is obtained from the PPG signal. The intricate and interconnected determinants of peripheral and central hemodynamic features, including vascular tone and stroke volume, are reflected in the PI determinants. Numerous research conducted recently have shown the intriguing functions of this variable, particularly in the evaluation of regional or neuraxial block success and hemodynamic monitoring in anaesthesia, perioperative care, and critical care. However, as of yet, no evaluation has been released regarding PI's interest in these subjects. The physiological and pathologic factors that determine PI will be discussed first in this narrative overview, followed by the mean used to calculate this number and any possible restrictions. The evidence that is currently available about the effectiveness of PI in various clinical settings, including operating rooms, critical care units, and emergency departments, will be given and addressed in the second section. Lastly, the viewpoints on the use of PI and the points that need to be investigated in relation to this instrument will be highlighted.

I. INTRODUCTION

Takuo Aoyagi, who died on April 18, 2020, created pulse oximetry in the 1970s by utilising red and infrared light transmission through tissues in accordance with earlier research [1]. The fields of anaesthesia, perioperative care, and critical care have seen an increase in interest in non-invasive macrohaemodynamic and microcirculation monitoring. The photoplethysmography (PPG) signal, which was previously limited to monitoring oxygen saturation for decades, is now a useful tool for monitoring hemodynamics. PPG is an inexpensive, quick, easy-to-use, non-invasive tool. PPG data interpretation, however, can be difficult. The early use of this multifunctional device for hemodynamic monitoring via PPG signal was flawed due to a significant ignorance of its drivers. Nonetheless, PPG signal analysis has benefited from renewed interest in recent years, and several studies in anaesthesia, perioperative care, and critical care have demonstrated the value of PPG [2-4]. Perfusion index (PI), which is the percentage of the pulsatile element of PPG among other PPG signal components, has been extensively examined and is a potentially useful tool for medical professionals. Therefore, to maximise its proper use and effectiveness, one must have a solid grasp of the PI and PPG determinants as well as its constraints. This review will go on to describe physiological factors of PI as well as physical concepts. A number of PPG evaluations have been put up, most notably regarding the respiratory fluctuations of PI, also known as Pleth Variability Index (PVI), and its uses [3, 5–7]. But none of the evaluations listed above concentrated on PI specifically. Since then, a number of fresh data sets have also been released. This study provides the clinical use of PI in the operating room, perioperative care, and critical care. It also includes the physiological and technological components of PPG and PI that physicians need to grasp.

❖ Measurement of Perfusion Index

- **Principles and mechanisms of photoplethysmography**

Conventional PPG works on the basis of measuring changes in tissue volume indirectly through changes in the absorption of light beams passing through the tissue. After entering a tissue, the oximeter probe produces red and ultra-red light beams whose transmitted intensities are converted into an electrical current by a photodetector [8,9]. The same approach applies to another PPG modality called PPG via reflection, which makes advantage of the tissue's light reflecting capabilities. After that, the photodetector is positioned close to the light source to gauge the

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incident beams' reflectance [10]. PPG often uses two wavelengths: infrared light (940 nm) and red light (660 nm), which are mostly absorbed by oxyhaemoglobin and deoxyhaemoglobin, respectively. Variations in infrared light absorption are used to obtain the PPG curve. Nonetheless, some PPG devices employ one wavelength, or sometimes more than two [11].

- **Components of Perfusion Index**

Absorption of light fluctuates during the cardiac cycle. The maximum absorption occurs during the systole, which is indicative of the dilatation of arteries caused by the systolic pressure—that is, the rise in arterial blood volume under the illumination. The photodetector first receives the signal, which is then divided into pulsatile and non-pulsatile signals. During systole, pulsatile fluctuations in light absorption are sometimes described to as "alternating current" (AC). AC is the total of the fluctuations in the diameters of the pulsatile vessels that the light beams travel through. It indicates variations in the absorbance or reflectance of the incident light beams caused by pulsatile vessels under variations in arterial pressure. After signal processing, the PPG curve shown on real displays depicts AC, which is obtained from the infrared light stream. In order to decrease signal artefacts and achieve restoration of AC, computer filters must process the raw signal that the photodetector received [8,12,13]. Conversely, constant absorption is known as "direct current" (DC), and it is from DC that AC fluctuates. DC is the same as light absorption from other tissues such skin, soft tissues, bones, and non-pulsatile capillaries and venous arteries. Currently, DC is not shown on standard oximeter monitors. The PPG curve can be considerably distorted by these manufacturer-dependent methods between manufacturers [8,9].

- **Calculation of Perfusion Index**

PI stands for the ratio, or AC/DC, of continuous light absorption to pulsatile light absorption. PI, sometimes known as "peripheral PI," was first employed in pulse oximetry as a high-quality signal indication [4,14]. On the other hand, PI reflects the fluctuation in local blood volume during systole and is dependent on both the local and systemic hemodynamic state. Therefore, non-invasive hemodynamic monitoring may be achieved using PI.

- **Perfusion Index's Physiological value**

Two investigations reported mean PI levels (± standard deviation) at the finger (in healthy awake participants) of 2.2% ± 2.0 and 3.5% ± 2.4 [15, 16]. According to this, AC only makes up 2% to 3% of DC. In terms of vascular physiology, this indicates that the blood volume underneath the sensor rises by 2% with each pulse.

However, it is challenging to suggest a trustworthy normal value for this parameter because of the large differences in normal values among healthy volunteers (from < 1% to > 10%).

- **Significance of Direct Current (DC)**

Any change in DC will cause a fluctuation in PI since PI is the ratio of AC to DC. Therefore, venous compression (by, for example, a finger clip) or soft tissues may reduce DC and raise PI. Similarly, congestion brought on by an excess of fluid in the world would have the opposite effect. PI value would also be impacted by limb position owing to variations in venous filling and, therefore, DC; if the limb is in a declive position (venous congestion), DC would rise, and if it is in a proclive position, DC will decrease [3]. From a physiological standpoint, DC is also not continuous; in patients breathing on their own or with mechanical ventilation, minor fluctuations in sympathetic tone and venous return are noted [17, 18]. Likewise, DC may alter in response to alterations in vascular tone, such as those caused by vasoactive medications (i.e., DC reduction in response to elevated vascular tone) [19].

- **Alternating current (AC)**

According to some writers, PI just serves as a stand-in for vascular tone. A reliable proxy for vascular tone, the central to toe temperature gradient, was found to be linked with PI by Lima et al. [15]. In fact, PI quickly rose in the occluded region following local vasodilation brought on by plexus or spinal anaesthesia. In patients undergoing general anaesthesia, alterations in vascular tone caused by vasopressors (i.e., a drop in PI as a result of norepinephrine infusion) also had a significant impact on PI [20–25]. In fact, a number of recent investigations have indicated that stroke volume, or SV, is yet another significant PI predictor. In babies, PI was connected with both cardiac output and superior vena cava flow [26–28]. Although such information is not included in these papers, reduced flow may be linked to elevated vascular tone. Healthy individuals were subjected to a lower body negative pressure by Van Genderen et al.

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[29]. As reported as median and interquartile, they saw a sharp decline in PI (from 2.2% [1.6–3.3] to 1.3% [0.9–1.7]), a drop in SV, and no discernible rise in the skin temperature differential between the forearm and fingertip. The absence of substantial changes in the skin temperature gradient between the fingertip and forearm may be attributed to temperature change inertia or the small research sample (25 male participants). This suggested that SV itself had an impact on PI in addition to the local vascular tone [29-35].

- **Local conditions**

Local perfusion is evaluated by PI measurement. Even for clothe locations, the PI value varies by a few centimetres depending on the measurement site [33]. Thus, both local and systemic macrohaemodynamic state have a significant impact on PI. Given that thermoregulation and non-thermoregulatory stimuli (such as nociception and exercise) mostly affect local vascular tone [36,37]. For instance, following cold exposure, PPG waveform variance varied significantly between the ear and the finger [38]. Another way that regional anaesthesia demonstrates the impact of local conditions is through the increase in PI measured in the blocked area following the procedure. This indicates a decrease in local vascular tone, which is linked to an increase in local blood flow and volume in the blocked area with each heartbeat. The rise in AC and PI values is being caused by both the decrease in vascular tone and the increase in local blood flow and volume. Although this hasn't been researched, it is anticipated that DC will rise in the blocked area along with other vascular tone alterations. PI is a tool for monitoring local hemodynamics in this scenario, not central hemodynamics. Similarly, a variety of local factors need to be taken into account when interpreting a PI measurement, including local compression of soft tissues, veins, and/or arteries, changes in external temperature, limb postures, and severe arterial abnormalities such obliterating arteriopathy. Peripheral PI in the aforementioned circumstances more closely represents local circumstances than the central hemodynamic state [11, 27]. But there was no change in basal PI between individuals with and without vascular illness (diabetes and hypertension). Conversely, depending on the test site, macrohaemodynamic state, or cardiac index, might affect PI value. In fact, for low cardiac output in babies, PI tends to be larger at the right hand than the foot, and inversely for high cardiac output [26]. All of these factors point to the significance of regional variations in perfusion on local PI values, which are due to changes in sympathetic response and central hemodynamic condition [39].

❖ **Clinical uses**

In a variety of therapeutic contexts, PI has been investigated in the operating room for patients receiving general or regional anaesthesia.

- **PI in evaluation of regional block success**

PI was originally employed as a predictor of the effectiveness of regional anaesthesia, with a rise in PI being used to identify vasodilation brought on by the suppression of sympathetic tone. In contrast to MAP and skin temperature, PI measured at the toe has been reported as the most sensitive and early predictor of successful sympathectomy and epidural anaesthesia [21, 40]. It has also been shown that PI modification is useful in paediatric patients undergoing general anaesthesia following neuraxial anaesthesia [23, 41, 42, 43].

- **PI in evaluation of neuraxial anaesthesia-induced haemodynamic variations**

A correlation was found (r = 0.66) between the fall in systolic arterial pressure and basal PI measured at the finger site in parturients undergoing caesarean birth following spinal-epidural anaesthesia [44]. In addition, baseline PI had a stronger relationship with a drop in MAP or systolic arterial pressure than baseline heart rate, MAP, or systolic arterial pressure. The optimum threshold value for baseline PI to predict arterial hypotension during spinal-epidural anaesthesia (defined as fall in systolic arterial pressure 25%) was 3.5%, and the area under the receiver operating characteristics curve for this prediction was 0.87 (95% CI 0.74-0.99, p 0.001). Subsequent research yielded similar findings using the same cut-off value [45]. Therefore, a pre-spinal anaesthesia PI value of more than 3.5% indicates a higher risk of anesthesia-induced hypotension. Given that vascular tone is one of the primary drivers of diastolic arterial pressure, one should anticipate that the baseline PI value would likewise precisely predict the drop in diastolic arterial pressure. None of these investigations, however, examined the relationship between baseline PI concentrations and the drop in diastolic arterial pressure. Low basal vascular tone is indicated by a high PI value at baseline. Consequently, in patients with low basal

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sympathetic tone, the drop in sympathetic tone brought on by spinal epidural is more likely to cause a decrease in the stressed volume, which in turn causes a decrease in SV and venous return. Therefore, PI is an easy-to-use measure for identifying parturient individuals who are at a high risk of arterial hypotension following spinal anaesthesia and have low sympathetic tone [46].

- **Prognosis and PI in anaesthesia**

Even after controlling for confounding factors, a sizable, recent, retrospective investigation demonstrated that intraoperative PI was time-dependently related to serious postoperative complications or mortality (lower levels being linked with poorer outcomes) [47]. It is yet to be determined if PI targeting during anaesthesia could enhance patient outcomes in randomised controlled studies.

❖ **Clinical uses in Critical Care (Emergency department and ICU)**

- **PI's Static and dynamic values in ICU patients**

More than 15 years ago, Lima et al. published the first research assessing PI in ICU [15]. It assessed how PI changed in critically sick patients with poor peripheral perfusion (i.e., capillary refill time > 2 sec or central-to-toe temperature differential 7 °C) as well as healthy volunteers. The authors of this study found a substantial linear link between changes in PI and the core-to-toe temperature differential as well as a significant exponential relationship between PI and the temperature difference.

- **PI and prognosis in Critical Care (Emergency department and ICU)**

In patients experiencing acute circulatory failure, a number of investigations have demonstrated the detrimental effects of persistent macrohaemodynamic and/or microcirculatory changes [48–50]. Therefore, it is highly predicted that PI readings or fluctuations would suggest significant and/or chronic circulatory disturbances in these individuals, with greater levels of sympathetic activation. Consequently, this concept has been validated by several studies, and the prognostic significance of PI has been assessed in critically sick patients across various clinical contexts (septic patients, post-cardiac arrest, hypoperfusion patients, emergency department patients, and newborns). PI values in the ICU enable differentiation between septic and non-septic patients as well as between survivors and non-survivors in various groups (e.g., septic patients, mechanically ventilated patients, etc.) [51]. Additionally, ICU mortality was substantially correlated with PI [51, 52]. After eight hours of resuscitation, PI was able to predict 30-day mortality in hypoperfusion patients more accurately than central venous oxygen saturation (ScvO2), lactate, and arteriovenous carbon dioxide gradient (P(v-a) CO2) [53]. Subgroup analysis revealed that, even after ScvO2 normalisation, PI (with a 0.6% cut-off) could be able to identify patients with the poorest prognosis and identify them for supplementary therapy, particularly those that target the microcirculation. This was supported by a recent study that found that after six hours after resuscitation, survivors' PI values were considerably greater than those of non-survivors', indicating that a rise in PI value during the first few hours of resuscitation is linked to a better prognosis [54]. It is hard to determine, nevertheless, if the improvement in microcirculation or macrohaemodynamics—that is, the cardiac index—is the primary cause of the observed difference in PI between survivors and non-survivors following first resuscitation. A prospective investigation has established the possible predictive significance of peripheral PI following cardiac arrest [55]. In this investigation, at day 30, within the first half-hour following the restoration to spontaneous circulation, PI was likewise considerably greater in survivors than in nonsurvivors. The same authors reported similar outcomes once again [56], with patients with greater PI showing longer survival and satisfactory neurologic function (cerebral performance categories ≤ 2). However, it is challenging to interpret the PI differences between survivors and non-survivors since the authors did not disclose the cardiac index or other characteristics, such as microcirculation variables. Performances of PI were assessed in a prospective trial for the purpose of triaging patients brought to the emergency room in order to estimate their mortality at 15 and 30 days [57]. In this investigation, PI had no bearing on mortality or hospital admission prediction.

In contrast to ICU patients, this population's low severity rate and poor PI power may account for this.

For the 24 hours following admission, a low PI (≤ 1.4%), as reported in newborns, was proven to be accurate in determining the severity of the disease [58,59]. More information on PI levels in pre-term babies was recently provided by a prospective

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research [60]. Therefore, PI appears promising in newborns and babies to quickly assess the severity of disease, and has already become the subject of a review [61].

The majority of studies are retrospective, with PI measurement at various time points and different cut-off values; as a result, the clinical use of PI as a prognostic tool needs more research, even though PI appears effective in differentiating septic from non-septic patients and survivors from non-survivors in the intensive care unit.

- **Dynamic changes of PI induced by heat**

In a more recent study, individuals arriving with a shock were monitored for microvascular responsiveness using PI and a heating challenge [62]. In comparison to shocked patients, healthy volunteers' PI at the earlobe was substantially greater. All non-septic patients (healthy volunteers, ICU-control patients, and non-septic shocked patients, i.e., cardiogenic and hemorrhagic) showed a comparable rise in PI value following the heating challenge. After the heating challenge, PI increased less in individuals experiencing septic shock than in non-septic patients. A non-significant trend was seen in the development of PI and PImax/min following the heating challenge in survivors as opposed to non-survivors in a small population. Physicians may be able to distinguish between septic and non-septic patients using PI changes and recognise individuals who have a bad prognosis.

Van Genderen et al. examined peripheral tissue perfusion, particularly utilising PI before and after rewarming, in a prospective observational research including patients undergoing therapeutic hypothermia following cardiac arrest [63].

❖ **Fluid Responsiveness**

- **PI and prediction of fluid responsiveness or fluid removal in ICU**

Using a passive leg-raising (PLR) test, Beurton et al. evaluated whether PI fluctuation could reliably predict fluid responsiveness in intensive care unit (ICU) patients, the majority of whom were on mechanical ventilation [32]. With an area under the receiver operating characteristics curve of 0.89 (95% CI 0.8–0.95), a sensitivity of 91% (95% CI 76–98%), a specificity of 79% (95% CI 63–90%), and an increase of PI > 9% generated by PLR predicted an increase in cardiac index > 10% induced by PLR. A further research that also shown that PI fluctuations during an end-expiratory occlusion test might aid in the prediction of positive PLR supported these findings [33]. Regarding spontaneous fluctuations in PI, the cut-off value of the relative PI rise during the end-expiratory occlusion test was; however, much lower (2.5%) than the PI values that are often shown on monitors today, which typically have just one decimal place. In order to predict weaning failure, other scientists used the similar association between PI and SV to study mechanically ventilated patients during a trial of spontaneous breathing (using the ratio of PI before weaning trial/PI during weaning trial) [64]. They noticed that trial failure was linked to a lack of rise in PI during the spontaneous breathing experiment. This shows that patients may be on the early vertical section of the Franck-Starling curve, i.e., fluid responders, when PI increases during the spontaneous breathing trial, and are hence at a decreased risk of weaning-induced pulmonary oedema. Additionally, during renal replacement treatment, PI and PI fluctuations have been utilised to predict hypotension during fluid withdrawal [65].

- **PI respiratory variations and prediction of fluid responsiveness**

Because deep general anaesthesia lowers the oscillatory components of the perfusion signal linked to sympathetic, myogenic, and endothelium-modulated activity, the variability of PI is modest under steady-state circumstances [66]. Thus, in this case, stroke volume fluctuations are mostly responsible for PI variations. PVI (Pleth Variability Index), also known as PI respiratory variations, has been extensively researched for its capacity to predict fluid responsiveness in patients on mechanical ventilation, particularly in the operating room. The tracking of PI changes as a stand-in for SV variations (or pulse pressure) brought on by positive pressure breathing forms the basis of the physiological concept.

Then, PI respiratory changes may be almost as accurate as pulse pressure variation in predicting fluid responsiveness [67, 68].

In order to estimate fluid responsiveness, a recent meta-analysis by Liu et al. showed that the PVI cut-off value, which ranges from 7% to 20%, depends on the population under study and the ventilation settings (such as an ICU, tidal volume, or positive end expiratory pressure) [69].

Additionally, PVI is significantly impacted by the measurement location (because it is derived from PI) and appears to be a more accurate predictor of fluid responsiveness when

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measured in the forehead, as opposed to the finger and earlobe, where it is less affected by vasomotor tone [70]. While a prior research demonstrated lower lactate levels and intraoperative fluid volume when employing PVI-guided fluid management, a recent randomised controlled trial that compared conventional management to hemodynamic peroperative management based on PVI value did not result in a shorter recovery period [71,72]. Consequently, more research is required to determine the significance of PVI value in the OT's hemodynamic management.

In the operating room, PVI may also be a reliable indicator of a child's fluid responsiveness when they are on mechanical breathing [73]. However, the outcomes of the studies conducted on children are inconsistent, necessitating more research to validate the precision of PVI in forecasting fluid responsiveness in the paediatric population [73–75].

- **Impact of PI use in haemodynamic management during anaesthesia**

It is still unclear if using PI for hemodynamic monitoring will enhance the prognosis of patients having surgery, even if evidence indicate that it is beneficial in this regard. There haven't been any well-planned research done up to now. An intriguing study described how an algorithm integrating pulse pressure variation and PI was used to guide the use of vasopressors and fluid administration (that is, in the event of a hypotension episode, fluids should be given if the PI value stayed constant for the fifteen minutes prior to the hypotension, and on the other hand, an increase in PI value should prompt the use of vasopressors). The application of this strategy was linked to decreased intraoperative fluid administration (4.3 ± 1.3 ml/kg/h vs. 7.2 ± 3.3 ml/kg/h, p = 0.003) and decreased arterial hypotension duration (7.7 ± 5.0 min vs. 17.1 ± 10.6 min, p = 0.003) [76]. Nonetheless, there are a number of issues with this study. Among other things, the control group did not have an algorithm, and the algorithm's use could have encouraged the early use of vasopressors rather than fluid challenge. We may presume that the results of another method with other variables and no PI would be comparable.

- **Impact of PI use in haemodynamic management in ICU**

PI and its early fluctuations are related to prognosis in the ICU. Particularly in septic patients, hemodynamic circumstances can be complicated, and PI can be challenging to interpret [35]. The reduced rise in PI following the heating challenge in septic patients suggests that PI might possibly represent microcirculation abnormalities [62]. Rapid PI variations studies, however, are still helpful in ICU patients with maintained microcirculation when one PI variable (such as PLR, fluid challenge, etc.) varies more than the others. Comparing the PI value across measurement sites may offer helpful insights about local perfusion; after all, certain regions may continue to have inadequate perfusion even after their macrohaemodynamic state (MAP, cardiac index, and ScvO2) returns to normal. Recently, we reported on the use of a modified urine catheter for urethral PI monitoring [77]. A steady, dependable signal that could gauge the perfusion of urethral tissue was provided via urethral PI monitoring. But in this study, we didn't particularly assess the impact of therapies (such fluid challenge, vasopressors, and blood transfusion) on PI value, nor did we compare urethral PI value with other measurement locations. Van Genderen et al. observed a trend towards less fluid administration and less organ dysfunction at 72 hours compared with a conventional regimen in a proof of concept study comparing an early peripheral perfusion-guided fluid therapy vs. standard of care in patients with septic shock (using capillary refill time, PI, skin temperature difference between forearm and fingertip, and tissue oxygen saturation) [78]. Hernandez et al. have confirmed these results through a Bayesian reanalysis of the ANDROMEDA-SHOCK Trial. They concluded that, in comparison to a lactate-targeted resuscitation strategy, peripheral perfusion-targeted resuscitation—that is, resuscitation guided by capillary refill time—may result in a lower 28-day mortality [79]. In the intensive care unit, resuscitation algorithms that use PI for tissue perfusion evaluation have also been presented [80]. Large-scale randomised controlled studies should evaluate the effects of such algorithms, which include PI, on the outcomes of critically sick patients in conjunction with other resuscitation objectives (e.g., cardiac index, mean arterial pressure, ScvO2, capillary refill time). But under these intricate circumstances (septic shock, hemorrhagic shock, etc.), a number of PI determinants (such as an increase in stoke volume brought on by fluid loading, a rise in vascular tone brought on by vasopressors, and/or the administration of inotropic drugs) may change all

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at once and suddenly. This might be a factor in PI's sudden and intricate alterations. In these circumstances, it is more likely that PI changes will be interpreted more properly as an early warning that calls for a reevaluation of the patient's hemodynamic condition, including stroke volume.

II. CONCLUSIONS

The majority of devices now provide PI, a PPG-derived variable that measures perfusion at the interface of central and peripheral perfusion. It seems to be a practical, non-invasive supplementary tool for doctors doing hemodynamic monitoring in anaesthesia, perioperative care, and critical care. Understanding its determinants is essential to understanding its variations. It is yet unknown if PI usage in resuscitation algorithms will lead to better patient outcomes.

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