AIM and Transdermal Optical Imaging

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Abstract

Cardiovascular parameters like blood pressure, heart rate, heart rhythm, and heart rate variability are highly useful in assessing patient health, disease risk, and response to treatment. However, technological limitations curtail their measurement in many cases. The recent development of transdermal optical imaging (TOI) technology has made it possible to extract high-quality blood flow information from conventional video of a patient's face and then use it to accurately estimate these cardiovascular parameters. TOI technology could thus be implemented on any device capable of capturing and processing video (e.g., any modern smartphone) and thus constitute a comfortable, convenient, and ubiquitous tool for measuring cardiovascular parameters.

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TOI builds upon remote photoplethysmography in part by using machine learning to extract robust blood flow information from video of the face. This signal can be used directly to compute heart rate, heart rhythm, and heart rate variability. Information from signal features containing blood pressure information has been combined with the help of machine learning to accurately estimate systolic and diastolic pressures. Further development of this technology is likely to enable the assessment of additional physiological parameters (e.g., respiration rate, SpO_2), disease risks (e.g., hypertension, diabetes), blood biomarker concentrations (e.g., cholesterol, HbA1c), and even mental health conditions (e.g., depression, anxiety).

With the necessary regulatory approvals and clinical trials, TOI-based tools would enable accurate, convenient, and contactless screening, diagnosis, and monitoring of patient health. They would revolutionize healthcare delivery through better access and efficiency and thus not only reduce costs but also improve health worldwide.

Keywords

Transdermal optical imaging · Smartphone · Blood pressure · Telemedicine · Remote health monitoring · Heart rate variability · Heart rate · Heart rhythm

1 Introduction

See Video 1.

1.1 Characterizing the Cardiovascular System: Benefits, Obstacles, and Breakthroughs

Cardiovascular parameters like blood pressure, heart rate, and heart rhythm are some of the most vital measures in clinical health assessment. Heart rate variability (the subtle variation in timing between one heartbeat and the next) provides insight into cardiovascular health and general wellness. Such measures are routinely employed in the medical setting and increasingly at home and elsewhere. While the benefits of comprehensive monitoring are becoming increasingly apparent, so are the technological barriers preventing cardiovascular monitoring from being used to its full potential.

1.1.1 Blood Pressure Measurement

Hypertension Screening, Diagnosis, and Management

Hypertension (high blood pressure) is a major modifiable risk factor for cardiovascular disease, with a global prevalence of over 30% [1]. There is an immense need to employ blood pressure measurement in screening, diagnosing, and managing hypertensive blood pressures down to target levels. Despite the importance of these activities, hypertension awareness, treatment, and control rates remain less-than-ideal in high-income countries (67%, 56%, and 28%, respectively) and very limited in middle- and low-income countries (38%, 29%, and 8%, respectively) [1, 2].

Awareness is limited by inadequate screening in the clinic [3], and the requirement for special equipment to measure blood pressure is an obstacle to opportunistic self-screening at home. Diagnosis proceeds according to algorithms that most often require home or ambulatory measurements in addition to clinic measurements, and the management of high blood pressure via lifestyle modification or medication calls for regular blood pressure measurement on an ongoing basis at home [4]. The daily home ("out-of-office") monitoring recommendation is to take two measurements in the morning and two in the evening with a cuff-based oscillometric device. However, such measurements remain uncomfortable, and the need for multiple measurements (to average out naturally occurring oscillations in blood pressure) is time-consuming. Such factors might reduce patients' willingness to monitor their blood pressure and hinder blood pressure control. Further, comprehensive blood pressure profiles are increasingly valued in characterizing hypertension [5]. However, the bulkiness cuff-based devices make them inconvenient to bring along outside of the home, thus limiting the ability to comprehensively monitor one's blood pressure over a range of daily activities (e.g., at work).

General Health Assessment

Blood pressure measurement is a primary tool in assessing patient health in the clinic. For instance, high blood pressure could indicate cardiovascular compromise (stroke or myocardial infarction), and low blood pressure could indicate the presence of shock (septic, cardiogenic, anaphylactic). Measurements are conducted by auscultation with a sphygmomanometer or by automated oscillometric devices. A limitation of these cuff-based tools is that they are potentially unsanitary, and they require staff to get close to patients (potentially increasing the likelihood of infectious disease transmission). Further, cuff-based tools cannot be applied remotely in telemedicine consultations, thus precluding a comprehensive health assessment for those without devices at home.

General Health Monitoring

Blood pressure is also monitored continuously and semicontinuously in the clinic. For instance, patients are monitored perioperatively to track depth of anesthesia and both perioperatively and postoperatively for complications (e.g., blood vessel rupture or sepsis) [6]. Continuous monitoring is conducted most accurately (albeit invasively) by arterial line. Noninvasive continuous alternatives include finger-based devices (calibrated by brachial cuff), although such devices are very costly. A frequent alternative to these invasive or costly methods when possible is semicontinuous monitoring via auscultation or oscillometric device. However, their disadvantage is that nurses must occupy more of their time taking measurements. It has been proposed that some patients monitored semicontinuously might be able to spend less time in hospital by self-monitoring at home after minor surgical procedures. However, the logistical hurdle of distributing (and later collecting) cuff-based devices could limit the practicality of this option.

Heart failure patients require regular out-of-office monitoring to ensure that their blood is being pumped adequately [7]. The comprehensiveness of the monitoring required once again raises concerns about the comfort and convenience of cuff-based measurements.

1.1.2 Heart Rate, Heart Rhythm, and Heart Rate Variability

General Assessment and Monitoring

Heart rate is an easily accessible clinical indicator of various conditions that may require further assessment. Abnormally fast heart rates (tachycardia, >100 bpm) could indicate dehydration, infection, or cardiogenic shock. Abnormally slow heart rates (bradycardia, <60 bpm) could indicate depressant effects from medication or that something is wrong with the pacing mechanism of the heart. Heart rate can be crudely assessed by palpation (requiring time and contact with the patient), but in the clinic it is most often measured by various specialized equipment (e.g., pulse oximeter, blood pressure monitor, electrocardiogram (ECG), or auscultation by a trained professional).

Heartbeat rhythm and regularity are also important health indicators. Gross irregularities in inter-beat intervals (e.g., complexes of premature ventricular contractions) constitute arrhythmias that could suggest greater risk of disease or require treatment. Conversely, when it comes to the subtle timing differences between heartbeats (termed "heart rate variability"), more variability implies greater responsiveness to blood pressure and respiratory fluctuations. Higher heart rate variability is prognostically favorable for various cardiovascular diseases [8]. Further, heart rate variability has recently been identified as one of the earliest physiological predictors of sepsis/infection [9]. Frequency analysis of heart rate variability can closely approximate the state of the autonomic nervous system (sympathetic-parasympathetic balance); increased spectral power at low frequencies relative to high frequencies suggests an increase in sympathetic tone [8]. Certain time domain measures of heart rate variability are also informative and are strongly associated with parasympathetic activity [10].

Heart rhythm irregularities can be detected by a trained professional using auscultation, but most often they are assessed by electrocardiography (ECG). Heart rate variability is most often measured by ECG. ECG is highly accurate but requires specialized equipment and the attachment of adhesive probes to the patient's chest to attain the highest-quality recordings. This requirement has largely limited such assessments to specialty care (e.g., cardiology, neurology) and made them impractical in large-scale screens, general health assessments, and remote consultations.

Stress Assessment

The appreciation that psychological stress has a major impact on health and general wellness is driving demand for more frequent stress assessment in more people. Psychological stress has been traditionally assessed through questionnaires. However, a growing literature has associated various permutations of heart rate variability with psychological stress, thus creating a quick, efficient, and objective method of stress assessment [11]. However, its potential is limited by the requirement for ECG equipment.

1.1.3 The Need for Technological Breakthrough

It is becoming apparent that more comprehensive monitoring of cardiovascular parameters could have immense benefits but that the inconvenience, discomfort, and inaccessibility of existing tools present obstacles to measurement. A technological breakthrough is needed to enable the creation of a new generation of tools that are more comfortable, more convenient, and more accessible to truly realize the full potential of maximizing health and wellness through the measurement of these parameters.

2 Transdermal Optical Imaging

2.1 Overcoming Measurement Obstacles with Transdermal Optical Imaging Technology

One solution that addresses all of these measurement obstacles is transdermal optical imaging (TOI) technology [12–17], which uses artificial intelligence to accurately measure cardiovascular parameters from video of a patient's face. The technology extracts a continuous pulsatile blood flow signal from video. This signal is rich in physiological information and interrelated throughout the body [18]. As such, it can be used to estimate parameters like brachial (upper arm) blood pressure [14, 16, 17], heart rate [13], heart rhythm, and heart rate variability/stress [13].

TOI technology has a basis in conventional video and thus can be implemented as software on existing computing devices (e.g., smartphones, tablets, or any other device capable of capturing and processing video), thus transforming them into measurement tools without the need for special equipment. Such tools would be contactless and thus could be used more comfortably than many existing tools. Tools using TOI technology could be conveniently employed anytime and anywhere, with measurements carried out comfortably, safely (e.g., without contact), and efficiently.

2.2 Scientific Foundations of Transdermal Optical Imaging

2.2.1 Biomechanics and Video Capture

TOI technology is a novel variant of a more than decade-old technique called remote photoplethysmography [19]. With each beat of the heart, blood is circulated throughout the arterial system and produces a pressure pulse (a small expansion of the arteries) that propagates through the arterial system [20]. As this pulse passes through the superficial arteries of the skin, the arterial expansion compresses microvascular blood toward the surface of the skin. This puts additional blood into range of ambient light that has penetrated the superficial layers of the skin. The additional hemoglobin in this additional quantity of blood absorbs more of this light (according to its absorption spectrum), and consequently less light reemerges from the skin. Melanin in the skin also absorbs light, but its concentration remains constant from moment to moment. These cyclical attenuations of light can be captured by a consumer-grade video camera to reproduce the pressure pulses occurring within the artery. See Fig. 1 for schematic.

Distance from the camera, motion, skin tone, and variable lighting conditions can also affect what the camera captures, and so software employing TOI technology addresses these issues at the video capture stage. Distance from the camera is approximately controlled by having the user place their head within a head-shaped outline on the graphical user interface, and a software-based face tracker will further warn the user if they are too close or too far away. Motion of the face relative to the camera is similarly tracked with software-based face detection; measurement will not begin, and ongoing measurements will be cancelled if too much motion is detected. Skin tone and variable lighting conditions are accounted for in part by calibrating camera exposure and white balance prior to the measurement. Measurements will not proceed, and ongoing measurements will be cancelled if there is insufficient lighting or too strong of a light gradient from one area of the face to the next. In this way, recording conditions are optimized and standardized.

2.2.2 Extracting Plethysmographic Signal from Video Using Artificial Intelligence

Some of the earliest variants of facial remote photoplethysmography averaged pixel intensity in the green channel and then filtered out noise in this raw signal with software-based digital signal filters [19, 21]. However, it was believed that much of this signal arose from mechanical (ballistocardiographic) movements of the head (the subtle periodic movement of the head caused by blood pulsing up through the aorta and into the head) rather than color fluctuations caused by arterial pulsation under the skin surface. Principal components analysis (PCA) [22] was used to try to address this issue by identifying components of the signal that oscillated from one moment to the next relative to video data in the red channel (relatively little red light is absorbed by blood hemoglobin, and so it might be used as a baseline against which arterial pressure pulse oscillations can be detected) [23]. Another approach called the chrominance method [24, 25] isolated pulsatile signal in each color channel individually. A limitation of these methods is that they tend to identify periodicity based on the signal frequency with the highest signal power and therefore remain somewhat sensitive to contamination from periodic movements of the head [24]. Others have developed mathematical models to try to account for (and separate) the individual contributions of hemoglobin, melanin, and shadows in the extracted signal based on knowledge about their absorption spectra and camera spectral characteristics [26]. However, this deliberate modeling technique has had only limited success (perhaps due to the difficulty of adequately modeling the complexity of these factors).

TOI technology builds upon these approaches to achieve highly robust signal extraction [12]. Like other methods, TOI tracks specific regions of the face and extracts information from the red, green, and blue color channels (using multiple colors helps create a more robust signal) (Fig. 2a). But unlike any other approach, TOI uses a computational model trained using advanced machine learning techniques to determine the relation between skin color changes and arterial pressure pulse oscillations from one moment to the next. TOI encodes color information in each pixel as multiple layers (or "bitplanes") of binary values (0 or 1) for each of the color channel (red, green, and blue), and this serves as input for the computational model. The model (previously trained to predict a continuous arterial pressure) then selects the bitplanes that best represent hemoglobin fluctuations to comprise the signal. This technique results in a high proportion of signal relative to noise (e.g., from variable lighting conditions or skin tone differences). A machine learning approach like this may account for additional

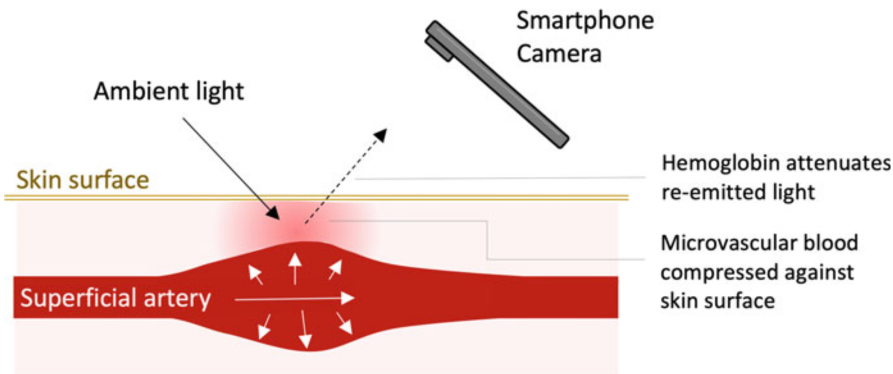

Fig. 1 Biomechanics and video capture for remote photoplethysmography. Pressure pulses created by the left ventricle of the heart arrive at the superficial arteries in the face. Here their expansion compresses microvascular blood toward the skin surface. The increased quantity of hemoglobin near the surface of the skin absorbs more incident ambient light (the specific wavelengths corresponding to its absorption spectrum), and consequently less of this light reemits from the skin. These subtle attenuations of light are captured by a conventional video camera as subtle skin color fluctuations

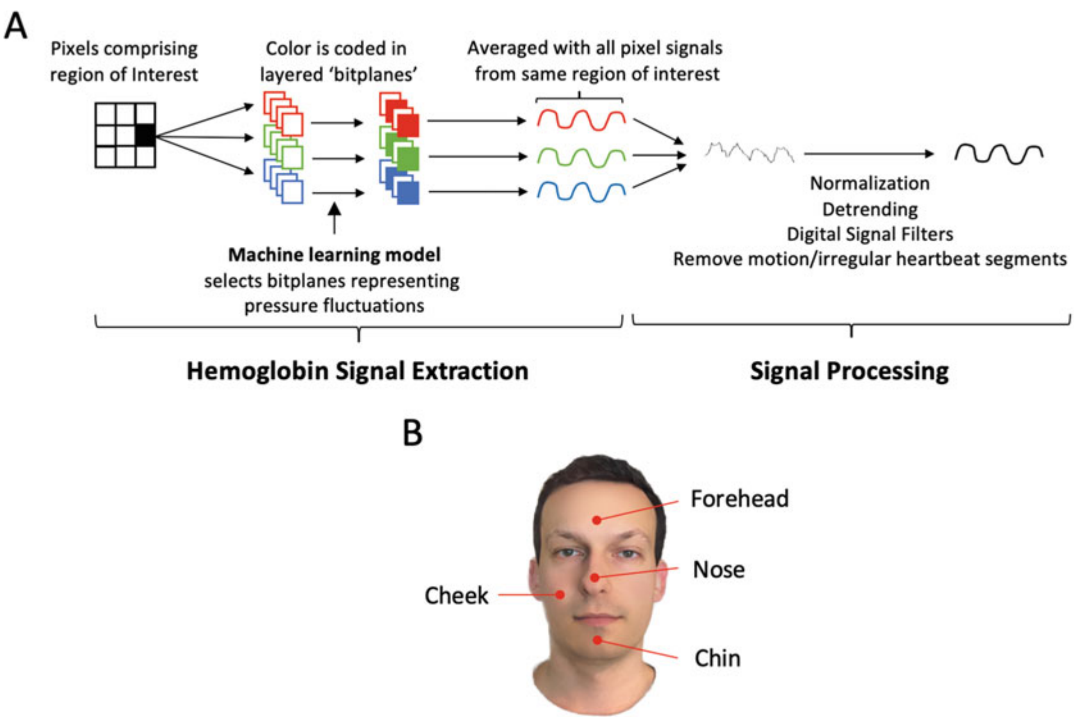

Fig. 2 Schematic of hemoglobin signal extraction and signal processing process (**a**) and major regions of interest (**b**)

complexity that is difficult to model with more deliberate techniques.

TOI further tracks multiple unique regions of interest (ROI) on the face (Fig. 2b). The reason for doing so is that different regions exhibit different spatiotemporal properties relative to ECG, despite all the pulses originating from the heart [12]. This is due to slight anatomical differences in facial vasculature, as well as the differential innervation of specific regions by either sympathetic or parasympathetic vasomotor neurons. For instance, sympathetic activity can strongly constrict subcutaneous blood vessels in the nose and lips and actively dilate vessels elsewhere like the forehead, cheeks, and chin [27]. Parasympathetic activity contributes to vasodilation in the lips and forehead. TOI thus captures rich information about the state of the vasculature and the autonomic nervous system that would be lost if signal from multiple regions of the face was simply averaged together. Finally, differences in temporal dynamics demonstrate that TOI signal is indeed driven by color changes rather than ballistic movements of the head [12].

After extracting raw signal in the red, green, and blue color channels, the signal is combined into a single raw blood flow signal (pressure pulse oscillation) for each ROI according to a special function [14]. During this process, each signal is normalized and detrended to account for variable lighting conditions. Digital signal filters (high, low, band-pass) remove low-frequency physiological oscillations (e.g., Mayer waves) and high-frequency noise. Signal elements suggesting motion and irregular heartbeats are also detected at this stage, and such segments are removed from the signal [17]. The final signal for each discrete region of the face is passed along to a variety of functions that extract information about physiological characteristics [14]. Some raw color information is passed along as well.

2.2.3 Cardiovascular Parameters and Their Relation to Blood Flow Features

Pulse Rate

Pulse rate corresponds to the patient's heart rate and is calculated as the number of pulses that arrive at the facial vasculature (from the heart). Pulses are counted as the number of major peaks within the signal segment and can be expressed as a frequency in hertz or a rate per minute [14].

Pulse Rate Variability

Pulse rate variability corresponds to the patient's heart rate variability, which is a measure of the variability in the intervals between heartbeats. Pulse rate variability measured by TOI closely tracks heart rate variability measured by ECG [13]. Pulse rate variability is calculated by detecting each pulse within the signal segment and then applying one several time domain calculations or frequency analyses that characterize the timing between pulses. For instance, the time domain SDNN measure of heart rate variability is calculated as the standard deviation of the interbeat intervals. A larger SDNN value indicates more heart rate variability.

Blood Pressure

Systolic and diastolic blood pressures can also be estimated using plethysmographic signal features. While many such features have been identified (e.g., augmentation index, pulse area) [28], no single feature has yet been found to provide enough information to accurately estimate blood pressure. It has thus been necessary to combine information from a variety of features to yield accurate estimates.

In an example of accurate blood pressure estimation, Luo and colleagues (2019) estimated blood pressure from a comprehensive set of 126 TOI blood flow features and 29 non-blood flow features [14] (Fig. 3). The blood flow features in that study and in a subsequent study by Yang et al. (2020) [17] can be divided into five groups: pulse shape, pulse energy (rates of change in pulse shape), pulse transit time, pulse rate variability, and pulse rate. **Pulse shape** features consisted of distances between various landmarks in the waveform, areas of certain sections within the waveform, or the ratio of one of these measurements with respect to another. Such features were calculated as means, maxima/minima, or measures of spread (e.g., standard deviation) across all pulse waveforms in the signal. **Pulse energy** features captured the rate at which certain pulse shape features emerged in the waveform as a function of time and were calculated as derivatives of pulse shape features. **Pulse transit time** is inversely related to the speed at which the pulse propagates across a fixed distance in the vasculature. It was approximated based on pulse waveform phase differences between two regions of the face. The propagation speed of pressure pulses is

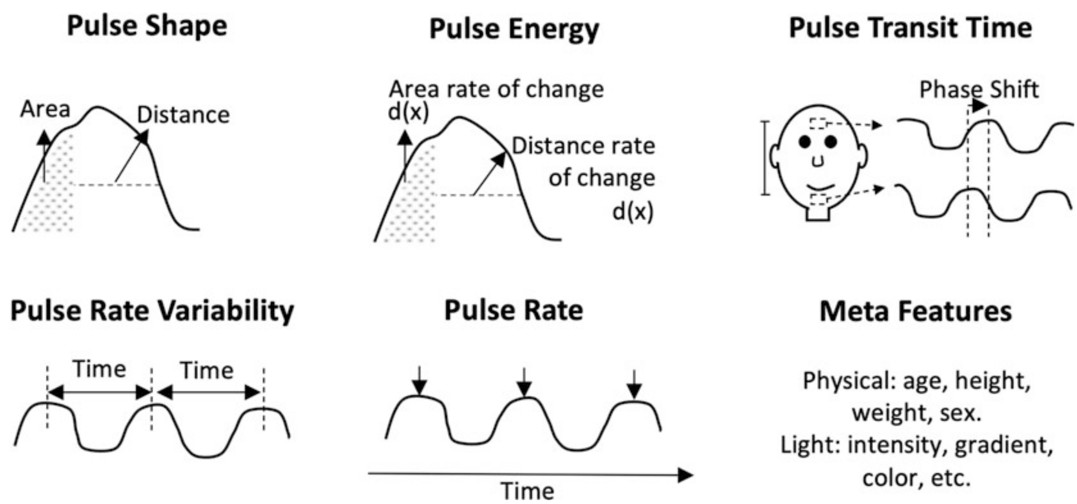

Fig. 3 Feature types used in predicting blood pressure

largely determined by arterial stiffness, and arterial stiffness is associated with blood pressure [28]. **Pulse rate variability** provides information about the state of the autonomic nervous system (sympathetic-parasympathetic balance), and greater sympathetic tone is associated with blood pressure increases [29]. Finally, **pulse rate** increases typically co-occur with blood pressure increases since both are key mechanisms for increasing cardiac output to meet the demands of the body. Thus, pulse rate contains information about blood pressure to the degree that it is signaling increases in cardiac output.

Non-blood flow ("meta") features included physical characteristics like gender, age, weight, height, race, and skin tone (as per the six-point Fitzpatrick scale), as well as features to help normalize for different lighting conditions (e.g., color information and lighting gradient information).

2.2.4 Predicting Blood Pressure Through the Efficient Combination of Feature Information Using Artificial Intelligence

The Luo [14] and Yang [17] studies extracted features from TOI signal and questionnaires and then input them into a computational model trained to predict either systolic or diastolic brachial blood pressures using advanced machine learning techniques. These models were trained to predict absolute brachial (upper arm) blood pressures and did not require prior calibration with a cuff-based device. Advanced machine learning techniques have thus been used as a method of efficiently combining information from multiple features to accurately predict blood pressure.

2.3 Present Advances Using Transdermal Optical Imaging

2.3.1 Accurate Blood Pressure Measurement

In their proof-of-concept study published in *Circulation: Cardiovascular Imaging*, Luo and colleagues demonstrated that combining the predictive power of multiple features makes it possible to accurately estimate blood pressure [14]. Their blood pressure prediction models trained using advanced machine learning techniques predicted systolic and diastolic blood pressures in a multiracial sample of subjects under controlled conditions when trained and tested on subjects within the normotensive systolic blood pressure range (those with a systolic blood pressure of 100–139 mmHg). Their models predicted with 94.81% accuracy for systolic blood pressure and 95.71% accuracy for diastolic blood pressure.

The average measurement error and its standard deviation were 0.39 ± 7.30 mmHg for systolic pressure and −0.20 ± 6.00 mmHg for diastolic pressure, which fall within a generally accepted measurement device limit of 5 ± 8 mmHg [30]. The feature novelty, feature diversity, and large dataset used in this study may have contributed to the high prediction accuracy in this study relative to other remote photoplethysmography approaches to measuring blood pressure.

This system was subsequently incorporated into a smartphone software application called Anura™ (Nuralogix Corporation) that adds additional controls to ensure good measurements under real-world conditions. Specifically, these controls further help account for motion, variable lighting conditions, and skin tone variations through camera calibration (exposure, white balance), measurement constraints (for motion, lighting, and signal quality), and signal normalization techniques [17]. This system is highly robust in accounting for real-world conditions and informing the user if measurement conditions are inadequate.

In a subsequent study, Yang and colleagues set out to expand the blood pressure prediction range of the models. To do so, they collected new data that included subjects with hypotensive and hypertensive blood pressures and then retrained the blood pressure prediction models on all the data (model performance in a given blood pressure range is largely a function of the quantity of training data in that range). These new models were trained against reference blood pressures measured by a trained observer using the auscultatory technique. As such, they were able to validate these new models in close conformity with internationally accepted blood pressure device validation guidelines published by the Association for the Advancement of Medical Instrumentation (AAMI) [30]. A published study of their preliminary work found that accuracy surpassed AAMI accuracy criteria for both systolic and diastolic blood pressures [17], with an average measurement error ± error standard deviation of −0.4 ± 6.7 mmHg for systolic blood pressure and 1.2 ± 7.0 mmHg for diastolic blood pressure (both were below the 5 ± 8 mmHg limit). This suggests that Anura is a viable blood pressure measurement tool for a range of blood pressures. A limitation of this work was that it was conducted entirely on Chinese patients, and it is yet unclear how this performance will translate to other races. The process of Anura blood pressure prediction is described in Fig. 4.

2.3.2 Accurate Heart Rate and Heart Rate Variability Measurement

Wei and colleagues (2018) validated heart rate and heart rate variability measured by TOI (as pulse rate and pulse rate variability) against heart rate and heart rate variability measured by the clinical gold standard ECG [13]. They quantified heart rate as pulses per minute and heart rate variability with the SD1/SD2 ratio. SD1 tracks “short-term” variability and SD2 tracks “long-term” variability; higher values of SD1/SD2 imply increased sympathetic activity [31]. Pulse rate measured by TOI was perfectly correlated with heart rate measured by ECG (Pearson r = 1.0) [13]. Pulse rate variability measured by TOI was highly correlated with heart rate variability measured by ECG (Pearson r = 0.89). TOI technology therefore captures all heartbeats and accurately captures the subtle variation in timing between them.

Sympathetic nervous system activity as reflected by increases in heart rate variability measures like SD1/SD2 ratio is associated with mental stress [32], and so it is apparent that TOI can also successfully track mental stress. The study results further imply that TOI can also capture gross rhythm abnormalities, although this has not yet been directly investigated.

These TOI-based measures have already been implemented as software-based tools. For instance, the Anura™ smartphone app (Nuralogix Corporation) measures heart rate, heart rate variability (SDNN), and mental stress (a proprietary stress score from 1 to 5 based on heart rate variability) and counts the number of irregularly spaced heartbeats (e.g., heartbeats suggestive of premature ventricular contractions) during its 30-s measurement.

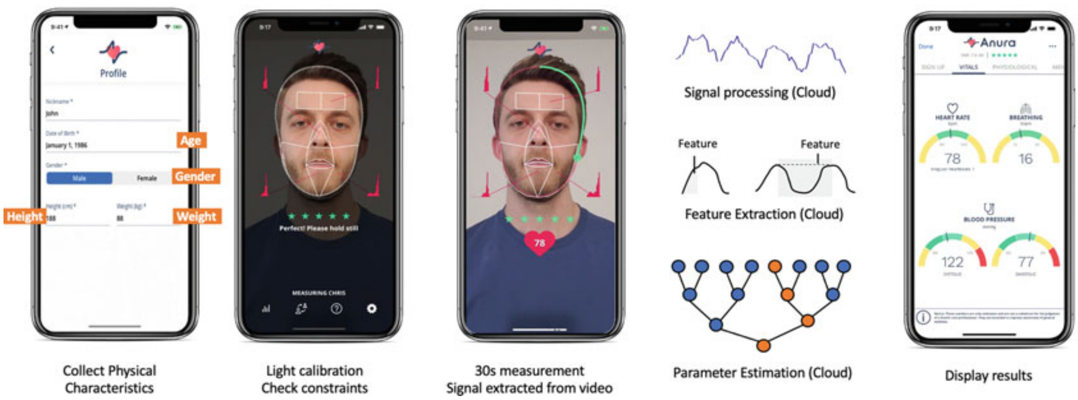

Fig. 4 Process of transdermal optical imaging in prediction of blood pressure with the Anura™ smartphone app (Nuralogix Corporation). Physical characteristics are collected on the profile screen during sign-up. Entering measurement mode triggers exposure and white balance calibration. Distance, motion, and lighting constraints are checked to ensure that conditions are adequate before beginning the measurement. A star-based signal quality system rates the lighting conditions (five stars indicate ideal conditions and will result in the most accurate measurements). The measurement will then begin and proceed for 30s. Blood flow signal is extracted from video during this time. Signal is then uploaded to the cloud for further processing and feature extraction. Machine learning-based models in the cloud estimate parameters. Finally, these parameters are downloaded to the phone and displayed to the user

2.4 Trends in Medicine and the Potential Impact of TOI

2.4.1 Growing Challenges for Healthcare Delivery

Population aging is expected to bring a rise in the prevalence of age-related chronic diseases (e.g., cardiovascular diseases), and this in turn will increase the need for comprehensive screening, diagnostic and monitoring approaches [33]. Such approaches help mitigate the health burden of disease, but they are highly resource-intensive when they are carried out in the clinic or long-term care home setting where they require time from primary care physicians and other staff. Growing primary care physician shortages in many jurisdictions will limit the ability to deliver this type of care. Concurrently, patients are demanding a more “patient-centered” approach to their care that is more convenient and gives them more control and involvement in their care. Issues with accessibility might further limit the ability to deliver high-quality and efficient care, particularly when it comes to remote communities and providing care safely during times of elevated infectious disease risk (e.g., when restrictions are in place for COVID-19).

2.4.2 Improving Healthcare Quality and Efficiency with Patient-Centered Health Monitoring

A shift from health monitoring in the clinic to self-monitoring at home would facilitate comprehensive monitoring of cardiovascular parameters like blood pressure and heart rate at reduced cost. Comprehensive monitoring maintains health and reduces costs associated with illness [34]. For instance, facilitating hypertension awareness and control greatly reduces the risk of cardiovascular diseases. Further, remote health monitoring in heart failure patients is credited with reducing costly hospital readmissions in heart failure patients by more than half through identifying complications early [35]. A shift away from clinic-based monitoring would improve convenience (via fewer trips to the clinic) and allow many with chronic diseases to remain in their own homes and in the community for longer before requiring care at a long-term care home [36]. Payers are realizing massive cost savings with such models and are increasingly incentivizing them in favor of costly long-term care arrangements [37, 38]. In fact, it is estimated that remote health monitoring will reduce chronic disease management costs by 10–20% or more. Finally, patients have shown a willingness to engage in patient-centered remote monitoring solutions for both health and wellness. Technological innovations in remote home monitoring will continue to be a major enabler for self-monitoring at home [33].

2.4.3 Improving Healthcare Accessibility with Telemedicine

Telemedicine is beginning to address issues of accessibility and convenience in medicine by assessing, diagnosing, monitoring, and communicating with patients remotely, most typically through video conferencing technology. Its use has been growing as a way to increase convenience (through fewer trips to the doctor) and provide high-quality care to remote communities. Most recently during the COVID-19 pandemic it has been used as a substitute for in-person visits to mitigate the risk of spreading infection. While the proliferation of ubiquitous high-speed internet and computing devices has enabled this technology, its application has thus far been limited by the lack of access to standard cardiovascular parameters (e.g., blood pressure, heart rhythm) that are commonplace in the clinic but most often cannot be measured at home. For telemedicine to reach its full potential, it will be necessary for measurement tools to match the ubiquity of video conferencing tools.

2.4.4 TOI-Based Tools Could Transform Personalized Self-Monitoring and Telemedicine

TOI technology has unique characteristics that would enable the creation of tools that address obstacles to measuring cardiovascular parameters at the patient level, as well as address wider challenges in healthcare delivery. Contactless measurement of blood pressure, heart rate, heart rhythm, heat rate variability, and stress via TOI would be much more comfortable than inflatable cuffs, ECG leads, or even wearables, for instance. Since TOI acquires pressure pulse information continuously, it can average out slowly oscillating physiological waves (e.g., Mayer waves) and determine blood pressure not only more precisely but in one quick measurement instead of the three long measurements required with cuff-based devices. Importantly, TOI technology could be implemented on any device capable of capturing and processing video. Such devices are already ubiquitous (e.g., smartphones, tablets, computers). Since the hardware required to run TOI is already everywhere (e.g., at home, at work, and on a video call with a doctor), measuring cardiovascular characteristics using TOI is highly convenient and does not require purchasing or carrying around extra equipment like wearables or often bulky cuff-based devices.

These improvements in comfort, convenience, and access to measurements have the potential to address challenges in healthcare delivery by facilitating patient-centered health monitoring and telemedicine (Fig. 3). TOI-based tools could facilitate a patient-centered approach and improve healthcare quality by making physiological measurements more accessible, more convenient, and more resource efficient. For instance, in the general public unaware of their blood pressure status, unprecedented access to clinical-grade blood pressure measurement right on one's mobile phone could facilitate the detection of abnormal blood pressure and help drive much-needed increases in hypertension awareness. Diagnosed hypertensives could benefit from increased comfort and convenience over traditional cuff-based devices in monitoring response to therapy. Facilitating regular measurements any time and any place (e.g., even outside the home) could provide greater awareness of high blood pressure triggers throughout the day and help drive increases in hypertension control (via lifestyle changes or medication). This would help address the massive health and financial burden of cardiovascular disease. More comfortable and convenient measurement tools are liable to drive further uptake of remote monitoring programs and thus reduce costs at the healthcare delivery level. TOI technology within telemedicine could enable the measurement of cardiovascular parameters that were previously not possible to measure over video calls unless the patient had specialized equipment at home. Such an advancement would drastically increase the utility of video consultations. A summary of TOI-based functionality is shown in Fig. 5.

2.5 Future Uses and Challenges for TOI

Given the tight interrelation between the cardiovascular system and other physiological parameters, plethysmographic signal acquired via TOI can further estimate additional parameters to varying degrees of accuracy. For instance, the expansion and contraction of the diaphragm during respiration exerts significant pressure modulations on the cardiovascular system and enables the quantification of respiration rate. The Anura smartphone app (Nuralogix Corporation) estimates respiration rate from plethysmographic signal, as do some clinical-grade pulse oximetry tools. Other health parameters convey information through the vascular system and might also be measured. They include blood oxygen saturation (by quantifying differences in the absorption spectra of oxygenated versus deoxygenated hemoglobin), blood biomarkers (e.g., hemoglobin concentration, cholesterol level, and even hemoglobin A1c [39]), disease risks (e.g., hypertension, diabetes mellitus, obesity), and even mental health conditions (e.g., depression and anxiety via the effects of autonomic activity on blood flow).

Employing TOI-based measurement tools in the clinic will require medical device approval from appropriate regulatory bodies (e.g., the Food and Drug Administration in the United States). These agencies commonly cite specific validation standards for blood pressure and heart rate monitoring equipment. However, such standards are technology-specific and currently there are no specific standards for remote photoplethysmography devices.

The most closely related blood pressure device standard from the Association for the Advancement of Medical Instrumentation (AAMI) [30] provides guidelines for validating cuff-based automated blood pressure devices against a gold standard reference device (e.g., auscultation by a trained observer). Despite technological differences, many features of this standard are likely to be translatable to TOI, including testing conditions, subject distribution requirements (for sex, age, and blood pressures), validation procedure, and accuracy requirements. A major accuracy criterion is that the mean error and error standard deviation between the systolic and diastolic blood pressures of reference and test devices fall below 5 mmHg and 8 mmHg, respectively. The technological differences between image-based devices like TOI and cuff-based devices may necessitate consideration of additional factors during validation like skin tone, lighting conditions, and motion, as such factors could conceivably impact measurements in an image-based system. Regulators have also recognized validation standards for heart rate measurement devices. For instance, the accuracy requirement for heart rate measured by a pulse oximeter is an error of less than 10% or ±5 beats per minute (whichever is greater) [40]. Once again, there are no guidelines specific for remote video-based technology like TOI, and so manufacturers will need to seek specific guidance from regulators on the validation approach to be used.

Finally, given the pivotal role of blood pressure and heart rate measurement in various clinical applications, it will be crucial to assess how TOI-based tools compare with existing standard techniques in terms of practical effectiveness. For instance, pragmatic trials might investigate how well measurements agree with existing standard methods and the impact of this on diagnostic or treatment decisions. With the necessary regulatory approvals and clinical trials, TOI-based tools will be able to provide accurate, convenient, and contactless screening, diagnosis, and monitoring of patient health. As a result, these tools will have the potential to revolutionize healthcare delivery by enhancing access and efficiency, which in turn will not only reduce healthcare costs but also improve the health of people all over the world.

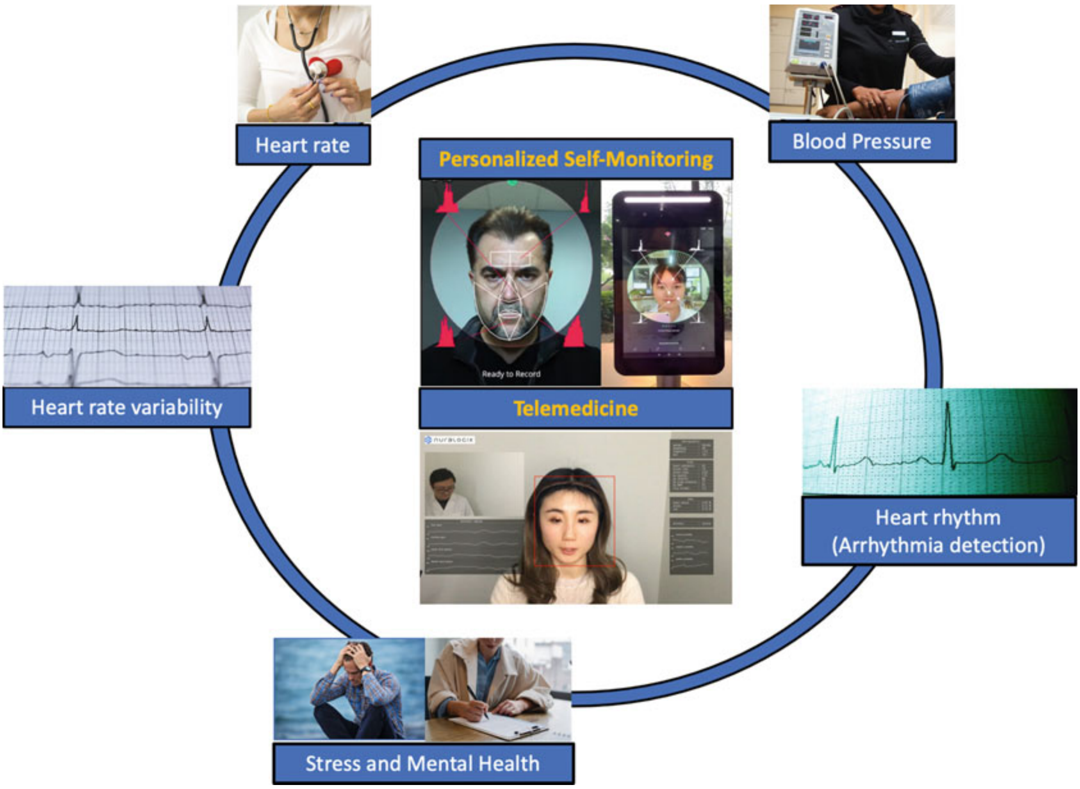

Fig. 5 TOI-based functionality in personalized self-monitoring and telemedicine applications. TOI has enabled the quick, comfortable, and convenient measurement of parameters like heart rate, heart rate variability, stress, blood pressure, and heart rhythm using already ubiquitous hardware like the smartphone

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