

# Spectral characteristics of longitudinal corneal apex velocities and their relation to the cardiopulmonary system

HT Kasprzak<sup>1,2</sup> and DR Iskander<sup>1</sup>

## Abstract

**Purpose** To study the naturally occurring kinetic characteristics of corneal surface.

**Methods** The right eyes of three subjects (young, early presbyope, and presbyope) were examined. Cardiac signal and longitudinal corneal apex movements were simultaneously measured with electrocardiography (ECG) and a high-speed videokeratoscope, respectively. Time, frequency, and combined time–frequency representations of the acquired signals were derived to establish their temporal and spectral contents. Coherence analysis was used to assess the correlation between the corneal apex velocities and the cardiopulmonary system.

**Results** In all measurements, longitudinal corneal apex velocity signals showed close correlation with the corresponding ECG signals. The signatures of the pulse frequency, which was inferred from the ECG spectra and their variations in time, were clearly visible in the spectral content of corneal apex velocities. For the young subject, the correlation was the strongest and all of the spectral content of the pulse signal including the harmonics was propagating to the corneal apex velocities. For the other two subjects, there was a clear propagation of the pulse signal itself but not of all pulse harmonics.

**Conclusions** Longitudinal movements of the corneal apex are closely related to the cardiopulmonary system. The differences in propagation of pulse harmonics to the corneal apex velocities for different subjects suggest that the frequency characteristics of apex velocity could be related to pulsative variations in the intraocular pressure and

biomechanical properties of the eye. These findings could potentially be used in noninvasive assessment of the hemodynamic status of the eye with high-speed videokeratoscopy.

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**Keywords:** longitudinal eye movements; high-speed videokeratoscopy; intraocular pressure; noninvasive assessment of the ocular pulse

## Introduction

Measuring ocular pulse is important in a range of medical applications where the assessment of haemodynamic status of the eye is required. For example, low amplitudes of the ocular pulse could indicate glaucoma and several other eye diseases, which may have vascular aetiologies.<sup>1,2</sup> The delays in the ocular pulse, on the other hand, could indicate the presence of severe carotid artery occlusive disease.<sup>3–5</sup>

There are invasive and noninvasive clinical techniques for measuring ocular pulse. Many of the invasive techniques are based on Goldman's applanation tonometer and its variants.<sup>6</sup> In ocular plethysmography,<sup>7</sup> for example, a pressure transducer attached to a suction device that is applied to an anaesthetised eye could detect both changes in the ocular pulse amplitude as well as the pulse delays relative to the fellow eye in unilateral carotid disease. This technique, although considered expensive at the time, was characterised by relatively high sensitivity and specificity.<sup>3</sup> Contemporary invasive methods combine the measurement of the intraocular pressure (IOP) and the ocular

<sup>1</sup>Faculty of Health, School of Optometry, Queensland University of Technology, Brisbane, Queensland, Australia

<sup>2</sup>Faculty of Basic Problems of Technology, Institute of Physics, Technical University of Hrocean, Wroclaw, Poland

Correspondence: DR Iskander, School of Optometry, Queensland University of Technology, Victoria Park Road, Kelvin Grove, Brisbane, Queensland 4059, Australia  
Tel: +61 738645644;  
Fax: +61 738645604.  
E-mail: d.iskander@qut.edu.au

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pulse amplitude as it is realised in the dynamic contour tonometry, where continuous and simultaneous registration of these two parameters is achieved.<sup>8,9</sup>

Techniques for noninvasive ocular pulse measurement have been proposed and include ultrasound imaging and laser interferometry.<sup>10,11</sup> Ocular pulse can also be monitored using more general noninvasive techniques for assessing hemodynamic status of the eye such as ultrasound Doppler imaging and laser Doppler flowmetry where, unfortunately, changes in the ocular pulse are detrimental to the quality of measurement of hemodynamics.<sup>12–14</sup> Northrop and Nilakhe<sup>10</sup> noted, that the ocular pulse can be described as ‘a minute, radial displacement of the corneal surface caused by arterial pressure pulsations in the ocular circulation acting on the compliance of the cornea’. This observation, however, has not resulted in optical noninvasive instruments that could be used in a clinical practice because, in the past, it was difficult to acquire accurately these ‘minute’ displacements.

Astakhov *et al*<sup>14</sup> were first to show correlation between the electrocardiographic (ECG) signal and longitudinal movements of the eye by utilising the effect of nuclear gamma resonance. They placed a radioactive material on the corneal surface and used the combined Mossbauer/Doppler effect to measure the longitudinal corneal apex velocity. Simultaneously to this measurement, they acquired the ECG signal and showed that the amplitude of corneal displacement can be related to the length of the cardiac cycle. There have been reports that how correlation between the ocular pulse and the heart rate. In particular, Trew *et al*<sup>15</sup> showed the mean pulse amplitude of the IOP to be inversely proportional to the heart rate and to be dependent on the subject position. On the other hand, Bosley *et al*<sup>16</sup> found close relationship between the ocular pneumoplethysmography waveform and the cardiac signal providing additional evidence towards the concept of cardiopulmonary-system-driven movements of the eye. However, the analyses of Astakhov *et al*<sup>14</sup> as well as Trew *et al*<sup>15</sup> and Bosley *et al*<sup>16</sup> were limited to time domain representations and no coherence analysis was used to find the synergy between the considered signals.

Earlier, Eisenlohr and Langham<sup>17</sup> observed that there is a relationship between the pulsatile change in the IOP and the resulting changes in the ocular volume. It is also well known that the corneal shape depends on the IOP, as it was established in numerous *in vitro* experiments.<sup>18,19,20</sup> On the other hand, natural changes in IOP are closely related to pulse and respiration.

Thus, as an example, taking the simplest approximation of the eye globe as a sphere where the volume is proportional to the radius cubed while changes in the volume are proportional to changes in

radius, we postulate that there must be a relationship between the ocular pulse and the speed of the observed radial displacements of the corneal apex similarly to that found between ocular pulse pressures and retinal vessel velocities.<sup>21</sup> These minute displacements defined by Northrop and Nilakhe<sup>10</sup> could be observed and recorded using digital camera systems equipped with appropriate optical magnifiers. Our work is motivated by the recent observation of longitudinal eye movements in high-speed videokeratoscopy<sup>22</sup> and their relation to the corneal shape.<sup>23,24</sup> In this work, we simultaneously measure cardiac electric cycle and longitudinal corneal apex movements and focus on the relationship between these two factors in a view of possible noninvasive measurement of the pulse with a high-speed videokeratoscope.

## Materials and methods

### Subjects

Three subjects participated in this study. The subjects did not have any corneal or eyelid pathology, had no symptoms of dry eye, and were not contact lens wearers. There was one young subject (25 years old), one with early signs of presbyopia (42 years old), and one presbyopic subject (58 years old). Only the right eyes of subjects were examined. The study met the requirements of the university human ethics committee.

### Measurements

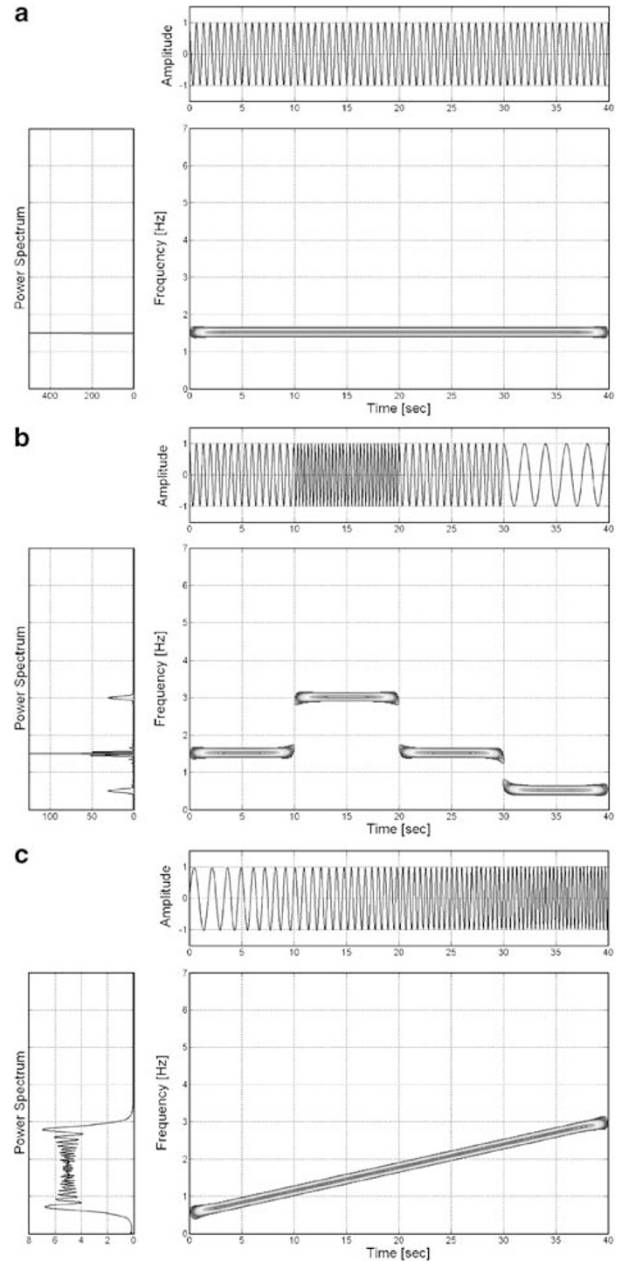
The cardiac electric cycle was measured with three bipolar leads (Einthoven’s triangle) connected to two wrists and the left ankle of a subject.<sup>25</sup> The resulting electrocardiographic signals were amplified using a bio-amplifier and collected with a MacLab/4s (ADInstruments Pty Ltd, Castle Hill, NSW, Australia). The sampling rate was set to 40 Hz. The longitudinal corneal apex movements were observed and registered at 50 Hz with a high-speed videokeratoscope based on the Medmont E300 unit (Medmont Pty Ltd, Melbourne, Australia). In short, the movements of the corneal apex could be observed by a high-speed videokeratoscope owing to the cone-side viewer embedded in the Placido disk cone of the E300 videokeratoscope. The cone side viewer is used to measure accurately the distance between the corneal apex and the imaging device of the instrument. More details on the high-speed videokeratoscopy and longitudinal eye movements can be found in our earlier works.<sup>22,24</sup> A specialised trigger was constructed to synchronise the simultaneous recording of electrocardiogram and longitudinal corneal apex movements on two separate computer systems.

The subjects were instructed to breathe on a metronome at a frequency of 0.5 Hz and fixate on the internal target of the high-speed videokeratoscope. For longitudinal corneal apex movements to be correctly acquired, it was necessary to use a specially designed solid headrest and a bite bar. The time of each recording was set to 40 s in which subjects were asked to try not to blink. For subjects' comfort, a drop of ocular lubricant was instilled to the eyes before each measurement. Recordings with a large number of blinks or poor quality of the tear film<sup>22,26</sup> were discarded from further analysis. Each recording was monitored during the measurement on the computer screens by an operator to ensure that there was no loss of fixation, no movements of the body that would interfere with the pulse measurement, and no additional external vibrations. The latter was an important factor as measurements of the corneal apex movements can be easily interfered by external sources such as closing the door in the other part of the building or running of water in pipes. Therefore, most measurements were conducted in early morning hours.

**Data analysis**

Time, frequency (Fourier), and time–frequency analysis of the acquired signals followed. The combined time–frequency analysis is an important tool for nonstationary signals (ie, signals with time-varying spectra) where spectral characteristics of signals do not provide unique representations.<sup>27,28</sup>

To understand the concept of combined time–frequency analysis and better appreciation of the series of plots presented in the next section, consider first a sinusoidal signal of frequency 1.5 Hz and its time–frequency representation given in Figure 1a. The top plot in the figure shows the familiar time representation of the signal, whereas on the left we show its spectrum. The main contour plot shows the combined time–frequency representation indicating that the frequency of the signal does not vary in time. Next, consider signals that change their frequency in time. Suppose a signal has an initial frequency of 1.5 Hz for the first 10 s, then the frequency increases to 3 Hz for the next 10 s, then it gets back again to 1.5 Hz, and finally falling to 0.5 Hz. The combined time–frequency representation of such a signal is shown in Figure 1b. Clearly, the spectrum alone (left plot) does not provide a unique representation. It indicates that there are three components (picks) in the signal and that the one at 1.5 Hz is the strongest but fails to show the exact frequency changes in time. On the contrary, the time–frequency representation uniquely shows these changes. To emphasise this feature of signal representation consider a signal that linearly changes its frequency from 0.5 to 3 Hz in the period of 40 s. The



**Figure 1** Concept of combined time–frequency analysis. Representation for a sinusoid signal (a), signal with discrete frequency changes (b), and signal with continuous changes of frequency in time (c).

combined time–frequency representation of such a signal is shown in Figure 1c. The spectrum alone, in this case, does not provide any useful information on the signal, except its frequency range, whereas the time–frequency representation shows the exact functional form of the frequency change in time.

Methodologies for dynamic signal analysis described earlier by Iskander *et al*<sup>29</sup> were utilised. In particular, the

Zhao–Atlas–Marks distribution<sup>30</sup> that has the property of resolving close spectral peaks in the time–frequency plane and provides clear representation for a wide range of signals was used.

It is important to note that in this work the variations in ocular blood flow were not directly measured. The frequency and time–frequency representations of the ECG signal would normally show a set of strong frequency components (peaks) corresponding to respiration, pulse, and its harmonics. Note that to stabilise the respiration frequency, the subjects were instructed to breath on a metronome at 0.5 Hz. Under this assumption, we could infer about the frequency content of the pulse signal directly from the frequency content of the ECG signal. This particular assumption was used also in other works that relate dynamic characteristics of the eye to cardiopulmonary system.<sup>31,32</sup>

The signal of the longitudinal corneal apex movement (displacement) is much more noisier than the ECG signal and may contain a few short peaks related to transitional loss of fixation due to saccadic movements or the blink control signal that was suggested by Doughty.<sup>33</sup> Although simple filtering techniques such as the median filter or the Savitzky–Golay filter<sup>34</sup> could be used as the preceding steps in spectral analysis, they are not appropriate in our application where we calculate the sample derivative of the signal, which is equivalent to the speed of the corneal apex movement. To derive the derivative of the corneal apex movement signal, we use a five-step filtering procedure consisting of: (i) calculating the derivative of the signal, (ii) thresholding, (iii) back integrating, (iv) smoothing with a five-point median filter, and (v) calculating the derivative of the smoothed signal. This procedure minimises the effect of sudden changes in the signal of the corneal apex movement on the spectra of the corneal apex velocity.

Time, frequency, and time–frequency representations of the corneal apex velocity were then inspected against the representations of the simultaneously recorded ECG signal. Coherence analysis was used to find the correlation between the ECG signal and the corneal apex movement. The coherence function  $C(f)$  is a function of frequency  $f$  and is defined as the ratio of the magnitude square of the cross-spectrum  $S_{XY}(f)$  between the two considered signals  $X$  and  $Y$  and the product of their magnitude autospectra  $S_X(f)$  and  $S_Y(f)$ .<sup>35</sup> That is,

$$C(f) = \frac{|S_{XY}(f)|^2}{|S_X(f)| \cdot |S_Y(f)|}.$$

In our application, signals  $X$  and  $Y$  denote the electrocardiogram signal and corneal apex velocity signal, respectively. The coherence function ranges from zero to one and indicates the synergy between the two

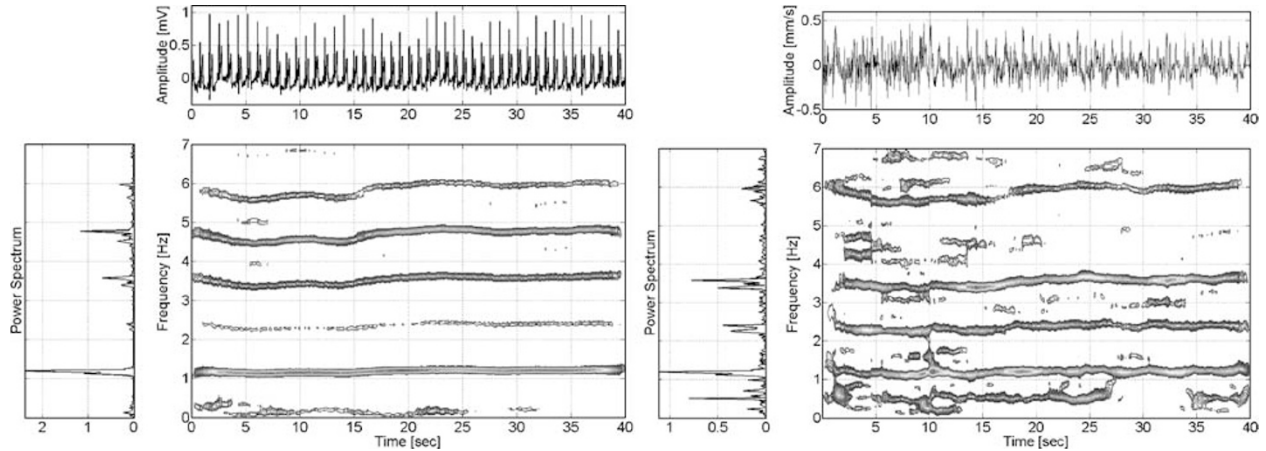
systems in the frequency domain. The coherence of zero indicates that two given signal components at certain frequency are independent while if the coherence value is one, they are perfectly correlated (ie, their phases change in time in the same way). As ECG was acquired at 40 Hz and the corneal apex movements were registered at 50 Hz, the ECG signal had to be interpolated before coherence analysis could be conducted.

## Results

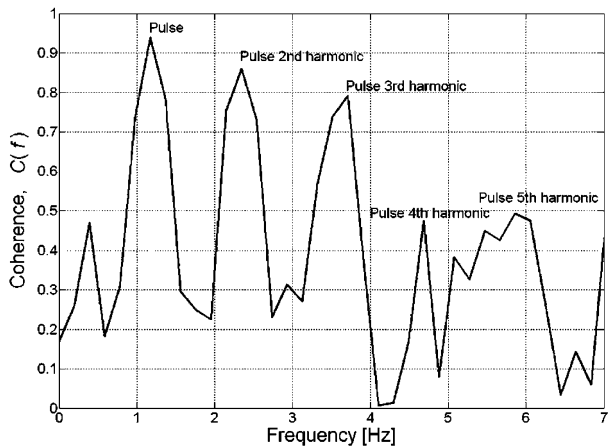
Several dozen measurements of ECG and longitudinal corneal apex movements were performed for each of the subjects. Several recordings had to be discarded from the analysis due to a significant amount of background noise in the apex movement signal.

For subject TL (the young emmetropic subject), the propagation of the inferred pulse signal to the corneal apex velocity appeared to be the strongest. In Figure 2, we show typical example of the time, frequency, and combined time–frequency representations of the recorded ECG signal and the corneal apex velocity derived from the corneal apex movements. The time–frequency representations clearly show that the spectra of both signals are not stationary and that the pulse (here centred at approximately 1.2 Hz) and its harmonic frequencies vary slowly in time, a feature that the spectrum alone is not able to represent. Note that the slow frequency variations in pulse signal and its harmonics are normally represented in spectrum as multiple peaks as it is indicated in Figure 2. We note that the ECG signal contains strong signatures of the pulse and its 3rd and 4th harmonics, whereas the pulse's 2nd and 5th harmonics have much smaller amplitudes. On the other hand, the corneal apex velocity signal shows strong signatures of the pulse, its 2nd and 3rd harmonic, and clearly visible 5th harmonic, whereas the 4th harmonic is residual. This suggests that not all frequencies can equally propagate in the cornea; some may be amplified and some be attenuated. Figure 3 shows the coherence function for the ECG signal and the corneal apex velocity, which shows that at the pulse and its first two harmonics, these two signals are strongly correlated,  $C(f) > 0.78$ , whereas at the 4th and 5th harmonics, they are also correlated but to a smaller extent,  $C(f) \approx 0.5$ . The coherence analysis clearly indicates that the observed frequencies in the corneal apex velocities are closely linked to the cardiopulmonary system.

In Figure 4, a typical example for subject HK (presbyope) is shown. An interesting feature of this subject is that the 3rd or 4th harmonic of the inferred pulse (here centred at approximately 1.3 Hz) was most often stronger than the 2nd harmonic and the pulse



**Figure 2** Time, frequency, and combined time–frequency representations (top plot, left plot, and contour graph) of the electrocardiographic signal (left) and the corneal apex velocity signal (right) for subject TL breathing on a metronome at frequency of 0.5 Hz.



**Figure 3** Estimate of the coherence functions for the electrocardiographic and apex velocity signals for subject TL breathing on a metronome at 0.5 Hz. We note that at frequencies related to the pulse signal and its first several harmonics, the two signals are strongly correlated.

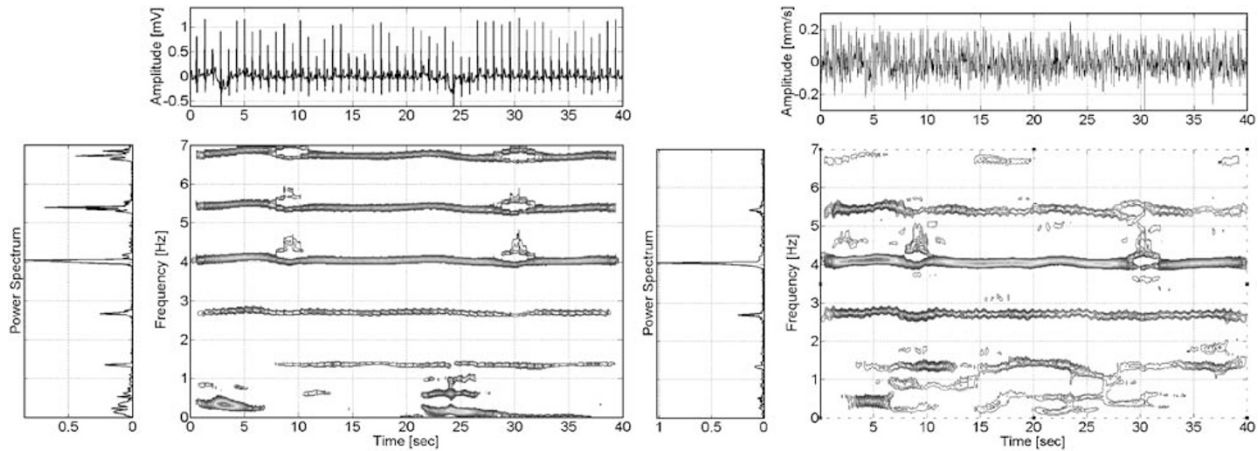
principal frequency in the electrocardiographic signal as well as in that of the corneal apex velocity. The particular example of signals from Figure 4 shows that the 2nd, 3rd, and 4th harmonics of the pulse have well propagated to the corneal apex velocity, whereas the pulse itself and the higher harmonics seemed to be suppressed. This is confirmed also in the coherence analysis (see Figure 5) where correlation at the pulse frequency between the ECG and the apex velocity is much weaker,  $C(f) = 0.395$ , than at the first three harmonics,  $C(f) > 0.88$ . It is also of interest that any instabilities in the ECG signal such as those observed at around 8th and 30th second of the recording (see the time–frequency representations in Figure 4) manifest themselves in a similar way in the

corneal apex velocity. This further confirms a very strong link between longitudinal corneal apex velocities and the cardiopulmonary system.

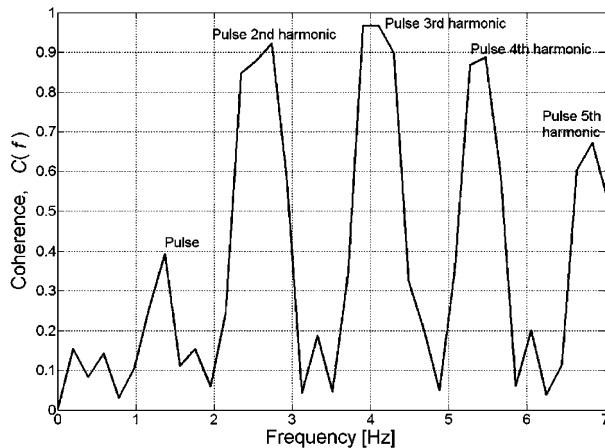
In Figure 6, we show a typical example for subject RI (a  $-5$ D myope and an early presbyope). The results show that for this subject, the spectral characteristic of the two considered signals are unlike those for subjects TL and HK. The signature of the inferred pulse (here centred at approximately 1.25 Hz) is the strongest in the ECG signal as well as in the corneal apex velocity. Interestingly, the 2nd harmonic of the pulse was always residual in the ECG signals, but it clearly manifested itself in the apex velocity signals. Only few higher harmonics of the pulse propagated to the corneal apex movements. The coherence analysis confirmed these findings. For the particular example from Figure 6, the coherence analysis showed strong correlation between the ECG and the apex velocity signals at signature frequency of the pulse,  $C(f) = 0.97$ , and its first harmonic,  $C(f) = 0.685$ , moderate correlation at 5th harmonic,  $C(f) = 0.5$ , and weak correlation at other harmonics of the pulse (see Figure 7). This last example shows the usefulness of coherence analysis, which does not depend on the strength of the given signal component but on its phase relationship with the corresponding component in the other signal. For example, we note that although the 2nd harmonic of the pulse was residual in all recorded electrocardiograms for subject RI, the coherence analysis showed that it correlated well,  $C(f) = 0.685$ , with the equivalent component in the corneal apex velocity.

### Discussion and conclusions

Longitudinal corneal apex movements were measured with high-speed videokeratometry whose resolution in



**Figure 4** Time, frequency, and combined time–frequency representations (top plot, left plot, and contour graph) of the electrocardiographic signal (left) and the corneal apex velocity signal (right) for subject HK breathing on a metronome at frequency of 0.5 Hz.



**Figure 5** Estimate of the coherence functions for the electrocardiographic and apex velocity signals for subject HK breathing on a metronome at 0.5 Hz. We note that at frequencies related to the pulse signal and its first several harmonics, the two signals are strongly correlated.

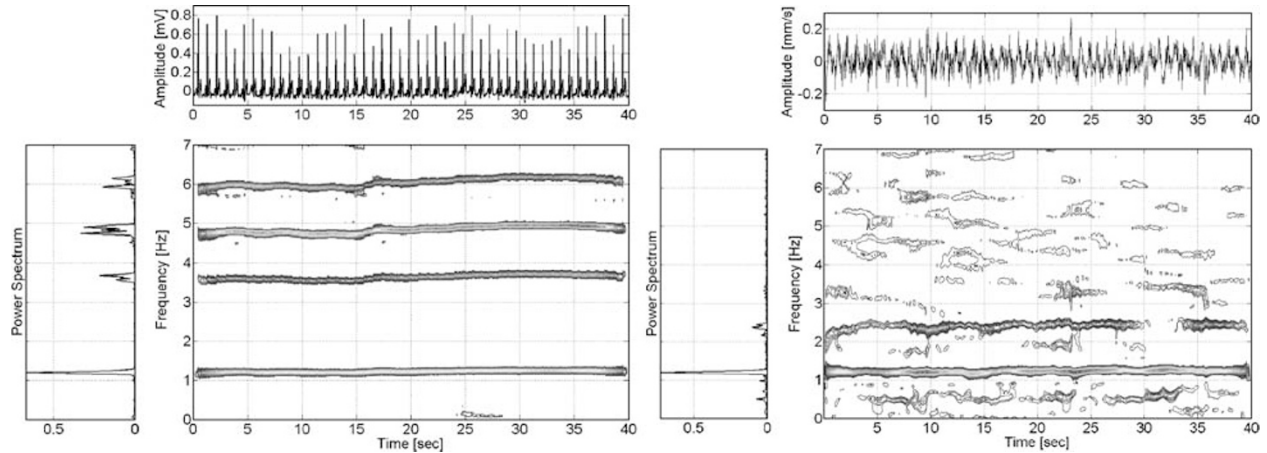
measuring apex distance was assessed in our earlier work at around  $10 \mu\text{m}$ .<sup>24</sup> The measurements of apex movement were then used to derive the corneal apex velocity which, in turn, can be affected by many factors such as pulsatile blood flow, IOP, corneal thickness, corneal rigidity, and refraction<sup>36</sup> (axial length of the eye). However, it is difficult to assess accurately many of these factors and in particular in the context of noninvasive dynamic measurement methodology. Using then a theoretical approach, we note that the corneal apex velocity should be related to changes in the ocular volume that in turn should be a function of changes in the IOP and the ocular pulse. As there exists some correlation between the ocular blood pressure and the

cardiac function,<sup>16,17</sup> it was of interest to see the extent of correlation between the ECG signal and the corneal apex movements.

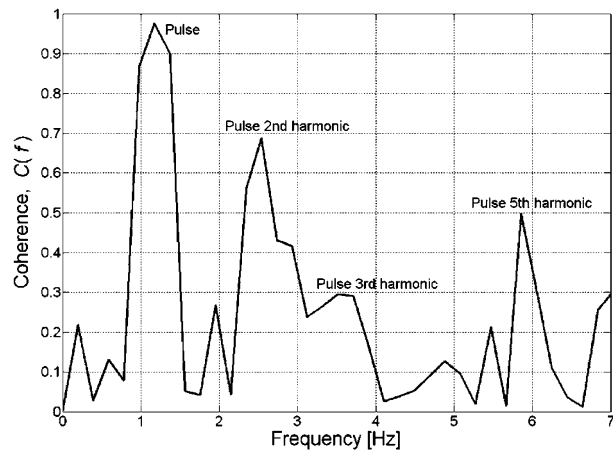
Our methodology can be viewed as a useful extension to methods of Astakhov *et al*<sup>14</sup> and Evans *et al*.<sup>2</sup> We used a new noninvasive tool (high-speed videokeratoscopy) and frequency analysis to establish the relationship between frequency content of the electrocardiographic signal and that of corneal apex movements. The results proved beyond doubt that the minute longitudinal movements of the corneal apex that we have earlier observed during high-speed videokeratoscopic measurements are closely related to the cardiopulmonary system. Moreover, the results have shown that by measuring longitudinal corneal apex movements we can not only derive the pulse signal but also infer about other characteristics of the cardiopulmonary system, providing more information on the haemodynamic status of the eye. We are not aware of any work solely dedicated to the comparison of the ECG spectra and those of the arterial pressure pulse. However, techniques for simultaneous acquisition of these signals have been reported.<sup>37</sup>

On the other hand, although in this study we have assumed that the major frequency components of the measured signals correspond to the pulse and respiration, it is hard to justify the assumption that all changes in the apex velocity were due to changes in pulsatile blood flow. As the correlation that we found was between the apex movement and an electrical signal, it could also be hypothesised that some components of the eye movements are controlled (not necessarily directly) by the electrocardiographic signal and that this link could play a role in the eye's visual processing.

Nevertheless, we were astonished by the similarities of the spectral representations of the acquired



**Figure 6** Time, frequency, and combined time–frequency representations (top plot, left plot, and contour graph) of the electrocardiographic signal (left) and the corneal apex velocity signal (right) for subject RI breathing on a metronome at frequency of 0.5 Hz.



**Figure 7** Estimate of the coherence functions for the electrocardiographic and apex velocity signals for subject RI breathing on a metronome at 0.5 Hz. We note that at frequencies related to the pulse signal and its first several harmonics, the two signals are strongly correlated.

electrocardiograms and corneal apex velocities in all three subjects selected for this study. For each of them, we have seen different propagation of the inferred pulse harmonics to the corneal apex velocities. The harmonics in the arterial pulse are related to vascular impedance, which depends on arterial viscoelasticity and properties of the blood.<sup>2,38</sup> This suggests that measuring the longitudinal corneal apex velocities and calculating their spectra can be also used in assessing some dynamics in the vascular status of the eye.

Finally, it could be envisaged that utilising high-speed videokeratometry to measure corneal apex dynamics, one would gain the ability to assess some of the eye diseases that may have vascular aetiologies,<sup>39</sup> in a similar

way to that of Evans *et al.*,<sup>2</sup> who used pneumatonometric continuous recording of the IOP and spectral analysis for identifying patients with glaucoma.

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