new dynamics of ageing
a cross-council research programme

Dynamics of cardiovascular ageing

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In brief

We gain wrinkles and lose hair, as we age, but our bodies also change in less obvious but much more important ways. This project studied the age-related alterations that occur in the cardiovascular system – the heart, lungs and network of arteries and veins that carry oxygenated blood and nutrients to every cell of the body and remove the waste products of metabolism. It was already known that the phase of breathing affects the rate at which the heart beats, but that this effect decreases as we age. The research has associated this reduction in heart-lung interaction with changes in the endothelium, the inner lining of all the blood vessels. It involved making non-invasive measurements of blood flow in the skin of 200 healthy subjects of all ages. The analysis focused on very low frequency oscillations in blood flow that can give a measure of the state of the endothelium. The main conclusions are, first, that to age healthily, you should look after your endothelium and, secondly, that it should be feasible to design an instrument for assessing endothelial health – an endotheliometer.

Summary of key findings

Our method of measuring the response of the endothelium to an external stimulus enables us to quantify its state of health. We have found –

- A decrease with age in the influence of the lungs on the heart, consistent with earlier work. It means that the cardiovascular system is gradually becoming less well able to function coherently as a single entity.
- That this change can be well-characterised and illustrated by computation of the cardio-respiratory "coupling function" (Figure 1).
- That there is a corresponding decrease with age in the extent to which the endothelium of blood vessels in the skin can react to a chemical stimulus. This reactivity can be taken as a useful measure of the health of the endothelium, and we were able to measure it *in-vivo,* directly and non-invasively.
- That one can thus define an individual's "endothelial age", which can be either less or more than their chronological age.
- No evidence of coherence between the slow oscillations underlying the heart rate and skin blood flow for frequencies below about 0.1 Hz. This suggests that the lower frequency oscillations, associated with endothelial function, are local in character rather than being under central control for the body as a whole.
- That the endothelium can also be stimulated by a rise in skin temperature, resulting in greatly enhanced low frequency oscillations. Correspondingly, a decrease in skin temperature reduces endothelial activity.
- It will be feasible to create a new medical diagnostic instrument based on a measurement of the endothelial response to temperature changes (patent application submitted). The intention is to design a device that will be the size of a large wrist watch. It will be strapped to the subject's arm for about ten minutes, and will make a series of measurements as the skin is first cooled and then warmed. Its output will be analysed automatically to give a measure of endothelial health. It will thus be easily useable by non-physicists.
- As an indicator of general health this endotheliometer has the potential to become almost as widespread in application as the clinical thermometer. We envisage their use by nurses, GPs, and other health professionals, as well as by hospital consultants. Conceivably, in the longer term given the price-reduction associated with mass-production, the endotheliometer could also be purchased by health-conscious members of the public.

Background

- The cardiovascular system, including the capillary system, is known to change during ageing. These changes are separate from the pathological effects of disease processes. Despite advances in the understanding of the cellular and molecular mechanisms of vascular ageing, functional studies of changes in blood flow over time, where multiple regulatory mechanisms act in combination, have been lacking.
- Functional studies in humans had previously not been possible due to the lack of available methodology for the analysis of the complex interactions involved in blood flow in the capillary bed, which is more complicated than flow in the much larger arteries. This type of functional study, in the ageing population, is important if we are to reach an understanding of the normal changes in microvascular function and the links between these changes and clinical pathology.
- Advances in sensor technology have opened up new approaches for non-invasive monitoring of the blood flow. Recordings of e.g. the electrocardiogram (ECG), respiration, blood pressure, and blood flow signals can be acquired and stored for later analysis by the application of a variety of sophisticated algorithms which we have generated. One important outcome has been an appreciation of the oscillatory nature of the blood flow through the capillaries and a detailed understanding of the components that contribute to this dynamic process.
- One of the lowest frequency (slowest) oscillations is associated with the activity of the endothelium, the very thin inner lining of all blood vessels. Our methodology enables us to follow this activity and how it responds to external stimuli *in-vivo,* directly and non-invasively.

Methods

The measurements involved 200 healthy adult volunteers of all ages (16–82). The subject lay on a bed and, once he/she was relaxed and comfortable, several different cardiovascular signals were recorded simultaneously over a period of 30 minutes.

The measurements included the electrocardiogram (ECG, showing the electrical activity of the heart), respiration, blood flow using a Laser-Doppler Flowmetry system with iontophoresis (chemical stimulant passed through the skin by a weak electrical current), arterial blood pressure, skin temperature and levels of oxygen in the blood. All of these measurements were recorded 400 times a second over the whole of the 30-minute measurement period.

The measurements taken confirmed dramatically the time-variable nature of blood flow processes. In an earlier era, simpler analysis techniques commonly worked by ignoring this variability, an approach that inadvertently discarded potentially valuable information. One of our major contributions to the field has been the development and/or application of new analysis methods, based around a branch of physics known as non-linear dynamics to take explicit account of this variability –

(i) Complexity and fractal analysis of heart rate variability (HRV), respiratory frequency variability (RFV), blood flow, and blood oxygenation signals. The complexity was independent of the mean and variance of a signal, and special techniques were required for its determination. Chaos theory provided meaningful ways of quantifying the complexity.

(ii) Wavelet spectral analysis of HRV, RFV, blood flow, and blood oxygenation signals. The use of wavelet analysis overcame two major difficulties in dealing with these signals: the time-varying nature of the characteristic frequencies; and the broad frequency band within which the characteristic peaks appeared. Our initial study had revealed age-related changes in each of the six frequency intervals mentioned above, thus providing a measure of how vascular function changes with age. With an increased number of subjects, we were able to seek statistically significant correlations between different intervals and to study how the inter-oscillator interactions changed with age, as revealed by the depth of modulation of one frequency component by another. Coherence analysis based on wavelets enabled us to study the interaction between different sets of simultaneously recorded data. Thus blood flow measurements with selective vasodilators, and temperature measurements, together with temperature perturbations to enhance oscillatory activity at the relevant frequencies, could be analysed in detail.

(iii) The coupling functions between heart and respiration were calculated (Figure 1), providing an excellent way of characterising their mutual interaction and how it changes with age.

(iv) Cardiorespiratory synchronization analysis was used as a complementary way of characterising the interaction between the cardiac and respiratory systems and their age-related changes. We used synchronization indices to quantify the degree of synchronization.

(v) Directionality analysis was used to establish the direction of the cardiorespiratory interaction. The analyses were based on both the phase dynamics and information theory approaches, as well as more recent approaches based on Bayesian inference and permutation information.

These methods provided us with an in-depth profile of the cardiovascular function of each individual. We have built a set of these profiles into a picture of how the profile changes during the process of healthy aging.

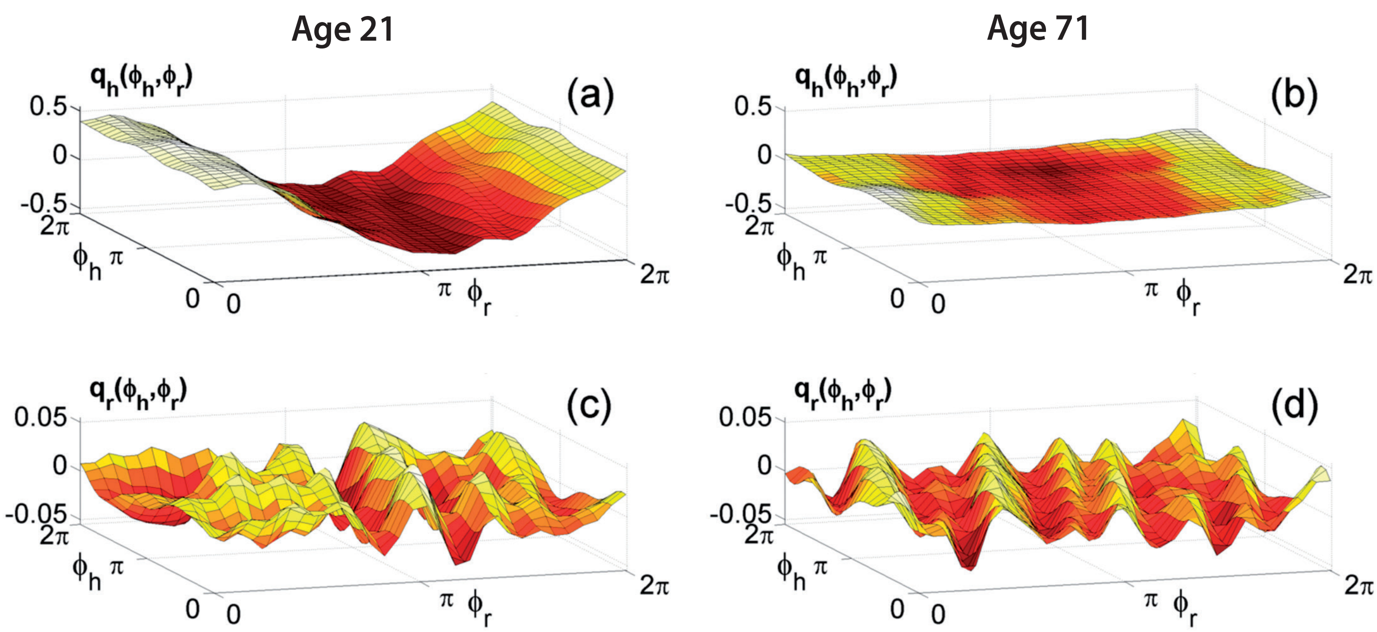
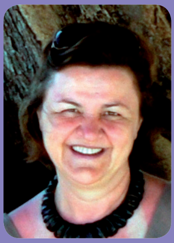


Figure 1. *Typical cardio-respiratory coupling functions in individuals aged 21 and 71. The influence of respiration on the heart decreases markedly with age, as shown in (a) and (b). But the opposite influence, of the heart on respiration shown in (c) and (d), hardly changes.*

Conclusions

- Our method of measuring the response of the endothelium (its reactivity) to a chemical stimulus has enabled us to study the ageing of the cardiovascular system.
- On average, endothelial reactivity declines steadily with increasing age. It is also known to be greatly reduced in several disease states, e.g. heart failure, hypertension.
- We found wide variation in endothelial decline between different individuals, however, with some older people having strikingly "young" endothelium and *vice versa.*
- It seems likely that diet and lifestyle play a large role in determining the rate of endothelial decline. So if you want to enjoy a healthy old age, the moral is "Look after your endothelium!".
- It appears feasible to design and manufacture a new medical instrument – an endotheliometer – that will provide for easy assessment of endothelial health by non-experts.



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