

CIRCULATION TIME IN MAN FROM LUNG TO PERIPHERY AS AN INDIRECT INDEX OF CARDIAC OUTPUT

Chris B. Wolff, Sophie K. Checkley, Georgina Bhageerutty, Himanshu Bhatt, Atholl Johnston, David J. Collier, Ilias Tachtsidis, N. Garvie, M. E. Rosenberg, and Nigel Benjamin

Abstract: Circulation time (Ct) between lung and periphery may be a surrogate for cardiac output, estimated here, for the most part, as the time between taking a breath of nitrogen and peripheral detection of a desaturation pulse. Use of pulse oximetry involves an internal, instrument delay; however, using the ear, we found shortening with exercise (12.1 ± 0.37 sec, at rest; 9.1 ± 0.25 sec at 100 watts), lengthening after β -blockade, and lengthening in patients with echocardiographic and clinical left heart failure (8 patients 16.2 ± 1.1 sec; 6 controls 12.0 ± 0.5 sec). Pulse oximetry failed, however, to discriminate heart failure from normal in several patients. In patients referred to a department of nuclear medicine for assessment of chest pain, pulse oximetry (finger and ear) showed unacceptable variability. Nuclide delays between lung and carotid artery correlated significantly with the reciprocal of gated SPECT estimated cardiac output (Q_{gs}); not so, however, for lung to finger. In normal subjects, an old Waters fast response oximeter gave short, reproducible Ct estimates and a significant correlation with the reciprocal of (indirect Fick) cardiac output (Q_{if}). The relationship for normal subjects was: $Ct = 0.28 \times 60/Q_{if} + 2.8$ sec (Q_{if} in L min.; P slope $< .001$).

1. INTRODUCTION

Wexler et al.¹ first measured lung to ear circulation time in 1946, well before pulse oximetry was introduced. The investigators showed that a desaturation pulse followed

inspiration of a large breath of nitrogen (N_2) after a delay of 4-5 sec. Recently, circulation time, measured by pulse oximetry, has been used to assess the severity of heart failure in hospitalised patients.² In this study, elevation of inspired oxygen was used and the authors suggested that circulation time might be useful clinically. Pulse oximetry should bear a similar, inverse relationship to cardiac output, as expected with fast oximetry, but pulse oximetry has an extra, uncertain instrument delay between the breath of N_2 and the instrument response. The presented work has appeared previously as an abstract.³

2. METHODS AND MODEL

2.1. Measurements

Ideally, fast oximetry would have been used in this study because of its simple, inverse relation to cardiac output. However, pulse oximetry was readily available and clinically acceptable.

2.1.1. Oximetry

A single breath of nitrogen was taken (timed by means of a pressure pulse from the airway or, initially, with a stethograph). Pulse oximetry was measured at the ear in both normal subjects and ambulant patients with left heart failure. Six normal subjects undertook rest and exercise measurements (pulse oximetry - ear) on different days, either following placebo or 100 mg atenolol, a β -blocker.

2.1.2. Patients with Chest Pain

Delays between arrival of nuclide at the lung and at the periphery (carotid artery and finger) were measured, as well as pulse oximetry (ear and finger). Gated SPECT⁴ outlines of the ventricles were obtained, allowing estimation of cardiac output (Q_{gs}). Q_{gs} and the delays were then related.

2.1.3. Fast Oximetry and Rebreathing Cardiac Output (Normal Subjects)

The Waters oximeter (Waters Instruments Inc., Model 0-500, Rochester, MN) pre-dates pulse oximeters; it has no internal delays. Lung to ear Ct and rebreathing Q (indirect Fick, Q_{if}) were measured, as in Eq. (1)⁵:

$$Q_{if} = VCO_2 / (CvCO_2 - CaCO_2) \quad (1)$$

The indirect Fick method depends on obtaining temporary equilibrium between mixed venous (pulmonary artery) PCO_2 ($PvCO_2$) and alveolar PCO_2 ($PA CO_2$) values. This is obtained by rebreathing, initially, from an oxygen-filled 6 L anaesthetic bag until PCO_2 has risen a little above $PvCO_2$. After 2 mins, the subject re-breathes again and PCO_2 in the bag falls to the mixed venous value, resulting in a brief plateau (mixed venous PCO_2). CO_2 content values are calculated ($CvCO_2$ and $CaCO_2$) from $PvCO_2$ and $PA CO_2$. The subject's CO_2 production rate is measured using a Douglas bag.

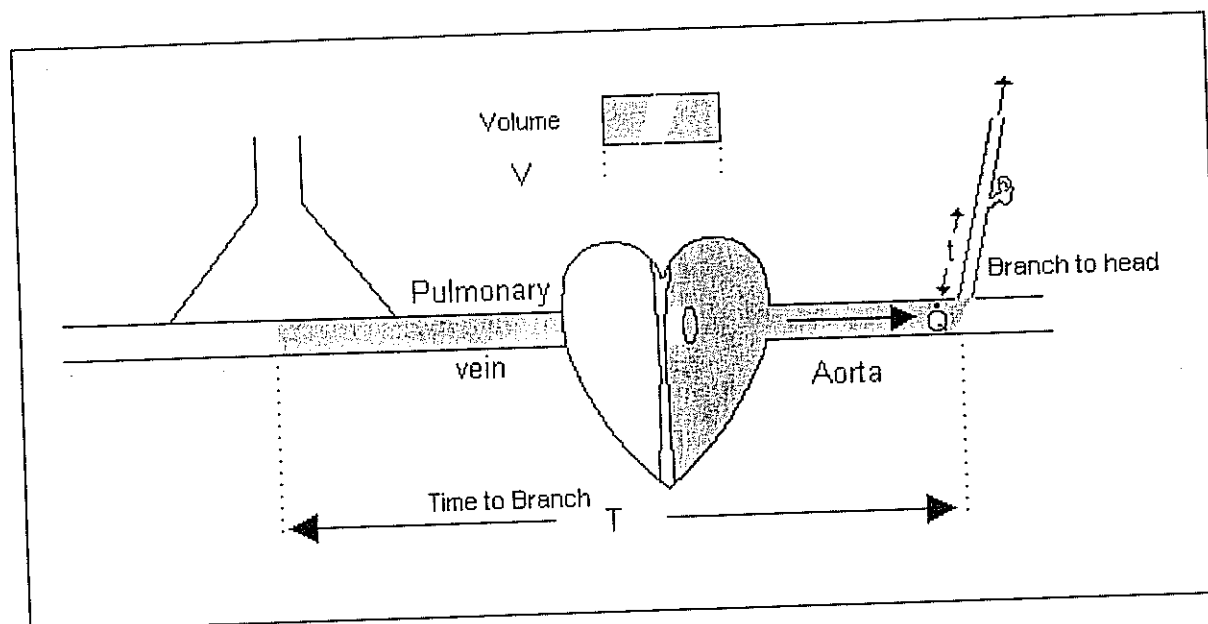


Figure 1. Schematic of lung, pulmonary vein, heart, and aorta, with vessels to the head and ear. Darker shading represents the volume of blood (V) in the circuit as far as the branch; T = the transit time; t = the delay between branching and arrival at the periphery (the ear in this case).

2.2. Model

Figure 1 shows a schematic illustrating the relevant pathway between lung and ear. C_t , the circulation time from lung to ear (as in Fig. 1), is $T + t$. The volume of blood in the circulation between the lung and the vascular branch from the aorta to the head, V , contains blood, which is all part of the total cardiac output. Since the time elapsing from blood passing through the lung and arriving at the branch point is T , cardiac output (Q) is V/T . Hence, we obtain $T = V/Q$. But C_t , circulation time, is $T + t$, where t is the transit time from the branch point to the oximeter on (in this case) the ear. If there is no internal oximeter instrumentation delay, then:

$$C_t = V/Q + t \quad (2)$$

Hence, it is possible, if both circulation time and cardiac output can be measured, to obtain an estimate of V (the volume of blood in the circulatory pathway between lung and aortic branch point; this will be the slope of a line fitting a plot of C_t against $1/Q$) and also of t , the transit time between the aortic branch point and the oximeter. The value t , being part of the cerebral circulation, is likely to be relatively constant.

With pulse oximeters, there is normally an internal instrument delay, but it is expected that various maneuvers will have predictable effects: exercise should shorten C_t while β -blockade may lengthen it; heart failure, with reduced cardiac output, should also lengthen it.

2.3. Experimental Series

The first series was of 20 normal subjects undertaking measurements with pulse oximetry (ear) at rest, at 50 watts and 100 watts. Two of these same subjects plus four

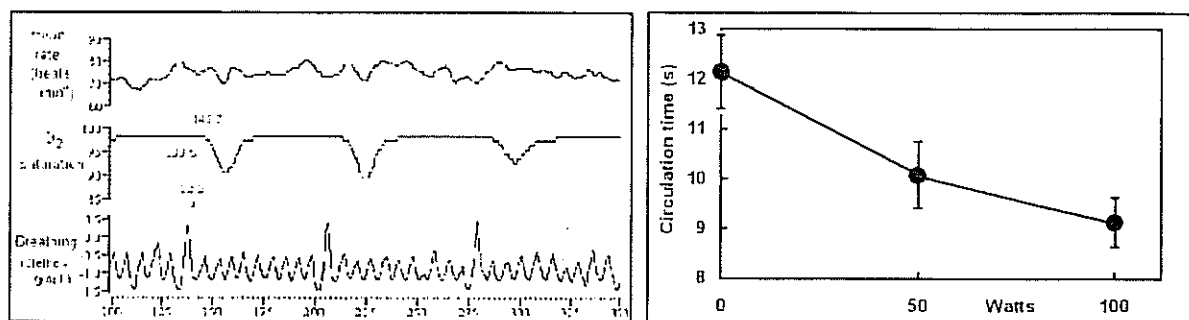


Figure 2. The left diagram shows respiration (stethograph), SaO_2 , and heart rate with pulse oximetry at the ear; the right figure shows the mean values from 20 normal subjects for lung to ear estimates of circulation time, at rest, 50 watts, and 100 watts exercise.

additional subjects compared measurements at rest and at 50 watts, either on placebo or on atenolol (separate days). Eight patients with clinically confirmed left heart failure⁶ were compared with 6 age-matched control subjects. Sixteen patients with chest pain had ear and finger oximetry, first pass nuclide and, separately, gated (ECG) SPECT cardiac measurements. Six normal subjects had fast (Waters) oximetry undertaken and, separately, rebreathing (CO_2) cardiac output measurements, both measured at rest and during 50 watts exercise.

3. RESULTS

3.1. Pulse Oximetry in Normal Subjects

Figure 2 (left) illustrates the effect of a moderately large breath of nitrogen on arterial oxygen saturation (SaO_2) at the ear. Mean values ($n = 20$) for lung to ear are shown on the right for rest and exercise (50 watts and 100 watts): rest = 12.1 ± 0.37 sec (\pm SEM); 50 watts exercise = 10.7 ± 0.33 sec; 100 watts exercise = 9.1 ± 0.25 sec.

3.2. Beta-Blockade and Left Heart Failure

Values for lung to ear circulation time (Ct, pulse oximetry) decreased slightly following placebo at rest, but did not fall in 50 watts exercise (Figure 3 - left and center panels). In contrast, these values increased following 100 mg atenolol, both at rest and in

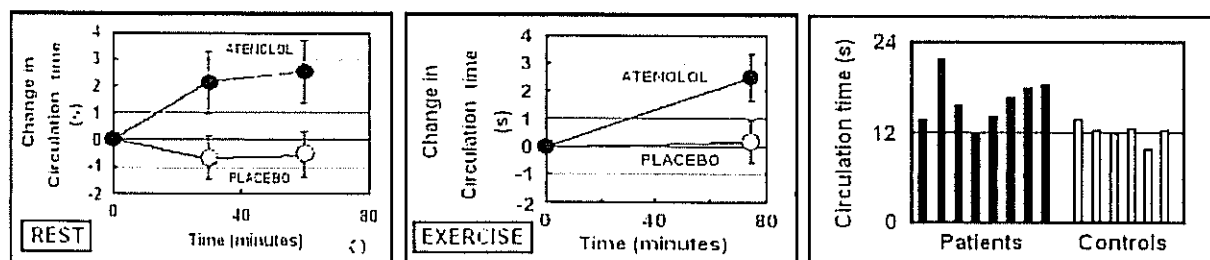


Figure 3. Mean (lung to ear) circulation time (\pm SEM) changes after β -blockade (atenolol, 100 mg) or placebo are shown for 6 normal subjects: left panel - rest; center panel - 50 watts exercise. Right panel: individual mean values for 8 patients with left heart failure are shown with values for 6 age-matched control subjects.

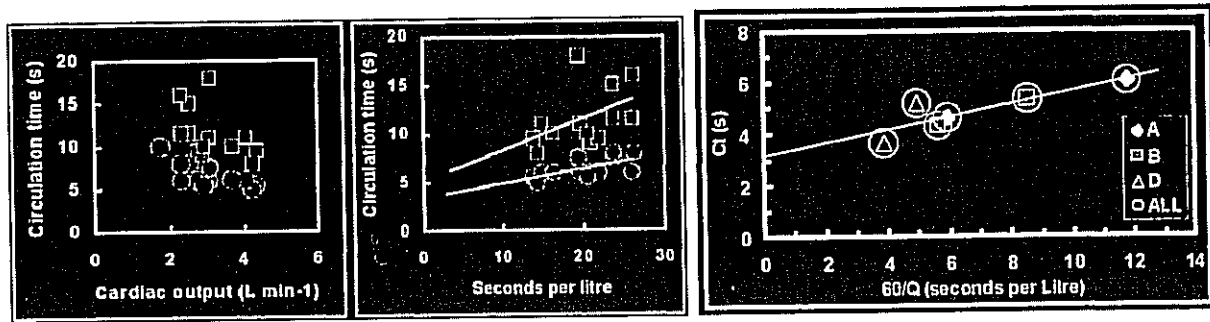


Figure 4. The left and middle panels show individual results for 16 patients referred to nuclear medicine for chest pain. The left plot is of two circulation times (delay between arrival of [1] nuclide at lung and carotid artery and [2] between lung and finger) versus cardiac output (Q_{gs} , gated SPECT estimate). The center panel shows these two circulation times plotted against $60/Q_{gs}$ (with best fit regression lines). Symbols: lung to carotid = \circ ; lung to finger = \square . The right panel shows Ct versus $60/Q_{ir}$ for normal subjects (Q_{ir} estimated from the CO_2 rebreathing method; only available for 3 of the 6 normal subjects, A, B, and D).

50 watts exercise. Changes were significant for rest ($P < .02$), but not for exercise ($P = .069$) due to an atypical subject result.

The use of pulse oximetry to assess left heart failure is also shown in Figure 3 (right panel). It is apparent that heart failure gives greater values, reflecting the lower cardiac output but with overlap between patients and controls.

3.3. Circulation Time and Cardiac Output

Since circulation time is $Ct = V/Q + t$ (see Eq. 2), a linear relationship is expected between Ct and $1/Q$. If cardiac output (Q) is measured in L/min, and Ct and t are measured in seconds, then the equation becomes:

$$Ct = V \times 60/Q + t \quad (3)$$

In Figure 4, the left and center panels relate to 16 patients referred to Nuclear Medicine with chest pain. They were monitored with first pass nuclide, giving circulatory delays (circulation times) between lung and carotid and lung and finger. These have been plotted against gated SPECT cardiac output estimates (Q_{gs}). The left panel shows the inverse relationship between the circulation time and Q_{gs} . The center panel shows the linear relationship between the circulatory delay and $60/Q_{gs}$ (sec/L of blood flow). The right panel shows Ct measured using the fast response (non-pulse, Waters) oximeter plotted against $1/Q_{ir}$, where Q_{ir} was estimated by means of the CO_2 rebreathing method⁵; valid Q_{ir} values were obtained in only 3 of the six normal subjects: A, B, and D. The relationship was found to be: $Ct = 0.28 \times 60/Q_{ir} + 2.8$ sec; Q_{ir} in L min; P slope $< .001$. Hence, $V = 0.28$ L, and $t = 2.8$ sec (from Figure 1 and Section 2.1.).

4. DISCUSSION

Exercise caused the expected trend in circulation time (a decrease) when measured with pulse oximetry. The conclusion of a direct relationship between Ct and $1/Q$ would be misleading from these data since there is an unknown instrumental delay. However,

cardiac output is known to increase with exercise and, as expected, Ct values were reduced. Furthermore, β -blockade is known to decrease cardiac output, so the increased Ct was also as expected. The measurements in patients with heart failure were, as a group, significantly longer than found in age-matched normal subjects. However, the potential diagnostic use of this technique was confounded by overlap, the longest values in normal subjects being greater than the shortest ones in heart failure patients.

Examining delays in the circulation and cardiac output using Nuclear Medicine methods confirmed the expected inverse relationship between cardiac output and circulatory delays across 16 individual subject rest values. Delays from lung to periphery using fast oximetry correlated well with $60/Q_{gs}$ (cardiac output in litres). Only CO_2 rebreathing cardiac output values from 3 of the 6 subjects showed adequate plateaus, but these gave a highly significant trend, supporting the theoretical Ct/Q relationship. The Waters oximeter was not suitable for clinical use, but these results on normal subjects, supported by the trends suggested by pulse oximetry and the nuclear medicine study, suggest that safe modern oximetry with a minimal instrument delay could be of clinical value as a surrogate cardiac output measuring device.

5. ACKNOWLEDGMENTS

Thanks are due to the Dunhill Trust for financial support, Mr. Ted Carter (Queen Mary and Westfield campus) for technical help, Georgina Lewis (Charterhouse Square campus) for help with patient recruitment, Steven Wilson, Cardiac Services Manager, for Echo-Cardiography services (Barts, Smithfield site), and to the technical staff in Nuclear Medicine at the Royal London Hospital. Thanks are also due to the Oxford University Physiological Laboratories for the loan of the Waters oximeter used in this study.

6. REFERENCES

1. J. Wexler, J. L. Whittenberger, and S. Himmelfarb, An objective method for determining circulation time from pulmonary to systemic capillaries by the use of an oximeter, *J. Clin. Invest.* **25**, 447-450 (1946).
2. B. Kasravi, J. P. Boehmer, and U. A. Leuenberger, A noninvasive method for estimating cardiac output using lung to finger circulation time of oxygen, *Am. J. Cardiol.* **82**, 915-917 (1998).
3. C. B. Wolff, S. K. Checkley, G. Bhageerutty, H. Bhatt, A. Johnson, D. J. Collier, N. Garvie, M. E. Rosenberg, and N. Benjamin, Circulation time in man from lung to periphery - pulse and non-pulse oximetry, *J. Physiol.* **543**.1, 41P (2002).
4. M. R. Mansoor, and G. V. Heller, Gated SPECT imaging, *Semin. Nucl. Med.* **29**, 271-278 (1999).
5. N. L. Jones, *Clinical Exercise Testing*, 4th edition (WB Saunders, Philadelphia, 1997).
6. New York Heart Association, in: *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*, 9th edition, edited by The Criteria Committee of the New York Heart Association (Little, Brown and Co., Boston, 1994), pp. 253-256.