Clinical Radiology 71 (2016) 940.e1–940.e5

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

A non-invasive cardiac output measurement as an alternative to the test bolus technique during CT angiography

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ARTICLE INFORMATION

Article history:
Received 19 October 2015
Received in revised form
7 March 2016
Accepted 10 March 2016

AIM: To investigate the association between a non-invasive cardiac output (CO) measurement and the scan delay, as derived from a test bolus injection protocol. The secondary objective was to determine which factors affect the relationship between the CO and scan delay.

MATERIALS AND METHODS: Fifty-five patients referred for a contrast-enhanced (thorax-) abdomen CT examination were included in this feasibility study. A test bolus examination was performed prior to the abdominal CT. During the test bolus injection, the CO of the patient was measured using a non-invasive finger-cuff measurement. Associations were analysed using linear regression analyses. Age, gender, height, weight, and blood pressure were included as potential confounders.

RESULTS: Linear regression analysis showed a negative and significant association between CO and delay. The regression formula was as follows: scan delay (seconds) = 26.8−1.6 CO (l/min), with a 95% CI between −2.3 and −1.0 ($p<0.001$). Weight appeared to be a confounder in this relation, and gender and blood pressure were effect modifiers. There was no interaction between scan delay and age, height and weight.

CONCLUSIONS: There is a negative and significant association between the non-invasive CO measurement and the CT scan delay; however, to validate these findings a larger cohort study is needed to investigate whether the non-invasively determined scan delay is as accurate as the use of a test bolus.

Introduction

Since the introduction of multidetector-row computed tomography (MDCT) the acquisition time for helical CT and CT angiography (CTA) has shortened. As a result, the total amount of contrast medium (CM) and the timing of CTA acquisition after administration of CM have become more critical in achieving the best contrast enhancement.[1]

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http://dx.doi.org/10.1016/j.crad.2016.03.007
0009-9260/

Vascular CT contrast enhancement is affected by multiple CM-related factors, including the volume of the iodinated CM, concentration, injection rate, injection duration, and the scan delay after CM injection. Patient-related factors affecting contrast enhancement are patient's age, gender, body weight, height, cardiac output (CO), and various pathological conditions.[2]

Reducing the amount of CM can be achieved by using the information extracted from a test bolus injection.[3] This method is based on injecting a small amount of CM (10–20 ml) prior to performing a diagnostic CT with a full bolus of CM. With the use of the test bolus, the time of arrival of the CM at the targeted position can be determined.[4] The test bolus injection results in a patient-specific scan delay and helps to adjust for individual variations in CT acquisition timing, and therefore, allows more efficient use of the amount of CM.

The time delay of CM arrival in the aorta after a test bolus injection is highly related to the patient's CO.[5] The CO can be measured continuously with the use of a non-invasive finger-cuff measurement (Nexfin monitor, BMEYE, Amsterdam, the Netherlands).[6] Age, gender, body weight, and height of the patient are used as input variables to adjust the Nexfin monitor for each patient. This method has been validated in both clinical and research settings.[7] By determining the relation between the CO and the time of arrival of CM after using a test bolus (i.e., scan delay), a non-invasive CO measurement could possibly replace the test bolus.

The primary objective of the present study was to investigate the association between a non-invasive CO measurement and the scan delay, derived from a test bolus injection protocol. The secondary objective was to determine which factors affect the relationship between the CO and scan delay.

Materials and methods

Study design

A total of 59 patients referred for a contrast-enhanced CT abdomen or CT thorax–abdomen examination were prospectively included in this feasibility study. The exclusion criteria were: allergy to CM, known arrhythmias or other heart disorders, impaired renal function (estimated glomerular filtration rate [GFR] $<$60 ml/min/1.73 m^2), age $<$18 years, and pregnancy or lactation. The study was approved by the institutional review board, and written informed consent was obtained from each patient.

Prior to CT acquisition the weight and height of the patients were noted and their body mass index (BMI) was calculated. The CM was injected via an 18-G intravenous cannula in the median cubital vein, using a dual-head CM delivery injector (OptiVantage Injection System, Tyco Healthcare Mallinckrodt, St Louis, MI, USA).

In this study, prior to the diagnostic CT examination, a test bolus injection was used to determine the time to peak of CM arrival in the region of interest (ROI) and calculate scan delay of CT acquisition. Diagnostic CT examinations were, however, performed with a fixed scan delay of 70 seconds.

Test bolus

The test bolus method is based on injecting a small amount (10 ml) of CM (ioversol 300 mg iodine/ml; Optiray 300, Mallinckrodt Medical, Petten, the Netherlands), followed by a saline chaser of 10 ml at 4 ml/s each. Directly after the test bolus injection, low-radiation dose scans (120 kV, 45 mAs) were performed every 2 seconds. A ROI was placed in the descending aorta at the level of the diaphragm to measure the contrast enhancement change in real time. As soon as the peak enhancement visually reached maximum enhancement, the acquisition was manually terminated. The dynamic series were evaluated with the use of dedicated software Syngo DynEva (Siemens Healthcare, Erlangen, Germany). A time-enhancement curve was obtained. The time to peak enhancement was used to determine the scan delay for CT acquisition.

Cardiac output measurement

During the test bolus injection, the CO of the patient was measured continuously with the use of a non-invasive finger-cuff measurement. Therefore, an appropriate-sized Nexfin finger cuff was applied to the mid-phalanx (Fig 1). The CO can be measured continuously by combining continuous blood pressure (BP) monitoring and a novel pulse contour method (Nexfin CO-Trek, BMEYE, Amsterdam, the Netherlands), which is based on the systolic pressure area and a physiological three-element Windkessel model. In this model, the effects of mean pressure and the influence of the patient's age, gender, body weight, and height on aortic mechanical properties are incorporated.[6] For every patient the CO, systolic and diastolic BP, and heart rate during the test bolus injection were recorded.

CT image acquisition

All CT examinations were performed using a 256-section CT system (SOMATOM Definition Flash, Siemens AG, Erlangen, Germany) with the use of tube current

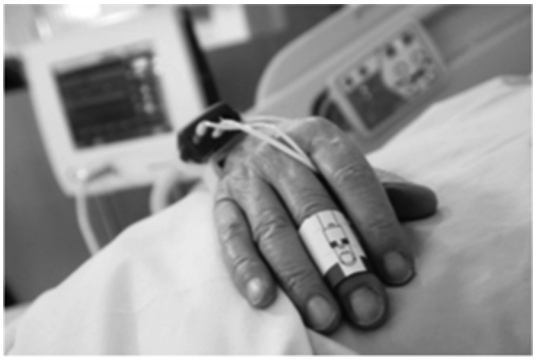

Figure 1 The Nexfin monitor (at the back) with the finger cuff attached to the finger. Figure derived from Martina *et al.*[8]

modulation software (CareDose4D). CT imaging parameters were: 120 kV tube voltage, 148 mAs reference output, 0.33 s rotation time, 256 × 0.6 mm beam collimation (128 × 0.6 mm, *z*-flying focal spot technology), 3 mm reconstruction section thickness, 1.2 helical pitch. All patients were scanned with the same CT parameters.

Statistical analysis

To determine the association between the CO measured with the Nexfin monitor and the scan delay, linear regression analysis was performed. Both crude and adjusted linear regression models were constructed. Age, gender, height, weight, and BP were included as potential confounders. A variable was classified as a confounder when the variable resulted in at least 10% change in the regression coefficient when included in the regression model.[9] In addition, possible effect modification was assessed for all covariates in order to investigate whether the association between CO and scan delay is different for different subgroups (e.g., men versus women). When the *p*-value of the interaction term was <0.1,[10] stratified analyses were performed and the results are presented separately for both subgroups. For analysis, BP was divided in three subgroups: low BP (RR ≤100/65 mm Hg), normal BP (101/66 mm Hg ≤ RR ≥ 140/90 mm Hg) and high BP (RR ≥141/91 mm Hg).[11] Associations were analysed using linear regression analyses. In addition, 95% confidence intervals (CI) were plotted for the resulting regression slopes. Statistical analyses were performed using SPSS 22.0 software (SPSS, Chicago, IL, USA). Values of $p<0.05$ were considered to be statistically significant.

Results

Study population

Fifty-four patients were included; five patients were excluded because their CO could not be measured with the use of the Nexfin monitor. The patients' characteristics are summarised in Table 1. The difference in men and women was well balanced (26 men, 28 women).

Association between CO and scan delay

Linear regression analyses showed a significant negative association between the CO and scan delay (Fig 2). The regression formula was as follows: scan delay (seconds) = 26.8−1.6 CO (l/min), with a 95% CI between −2.3 and −1.0 ($p<0.001$). The prediction intervals for the different COs with corresponding scan delays are summarised in Table 2.

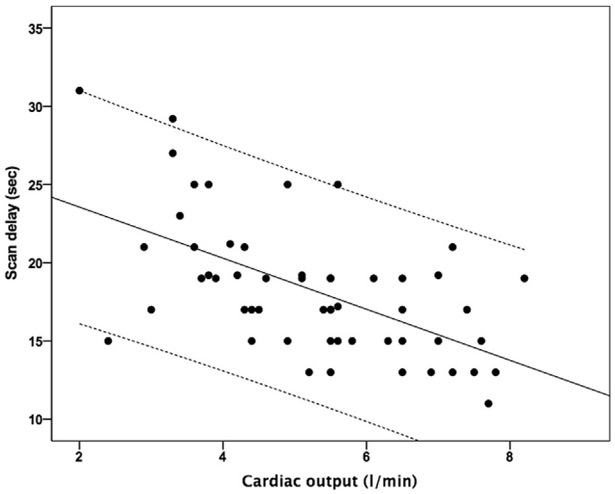

Figure 2 Scatter plot of scan delay versus CO showing a significant negative association between CO and delay. The regression formula was as follows: scan delay (seconds) = 26.8−1.6 CO (l/min), with a 95% CI between −2.3 and −1.0 ($p<0.001$). Ninety-five per cent CIs (dotted fitting lines) are fit to the regression line.

Weight appeared to be a confounder in the relationship between CO and scan delay. After adjusting for weight, the association between CO and scan delay increased, with the following regression formula: scan delay (seconds) = 20.2−2.3 CO (l/min), with a 95% CI between −2.9 and −1.6 ($p<0.001$).

Subgroup analyses

There was a significant interaction between gender and scan delay, and between BP and scan delay. Therefore, the results for the corresponding subgroups are presented separately. There was no significant interaction between scan delay and the other covariates age, height and weight ($p>0.1$ for the interaction term).

Gender

A significant interaction between gender and scan delay was found in the analyses ($p=0.04$; Fig 3). Therefore, the association appeared to be different for men and women. For men, the association between CO and scan delay increased (β: −2.4, 95% CI: −3.2 and −1.6, $p<0.001$)

Table 1
Patient's characteristics.

Patient characteristics	Mean ± SD
Age, years	61.4 ± 11.2
Body height, cm	170.5 ± 11.1
Body weight, kg	78.8 ± 14.7
Cardiac output, l/min	5.3 ± 1.5
Heart rate, bpm	68.6 ± 12.5
Systolic blood pressure, mmHg	143.6 ± 23.7
Diastolic blood pressure, mmHg	80.5 ± 11.5
Scan delay, seconds	18.2 ± 4.3

Table 2
Prediction intervals for the different cardiac outputs (COs) and corresponding scan delays in seconds.

CO, l/min	Scan delay, seconds
2 ≤ CO < 3	15–31
3 ≤ CO < 4	17–29
4 ≤ CO < 5	15–25
5 ≤ CO < 6	13–19
7 ≤ CO < 8	11–21

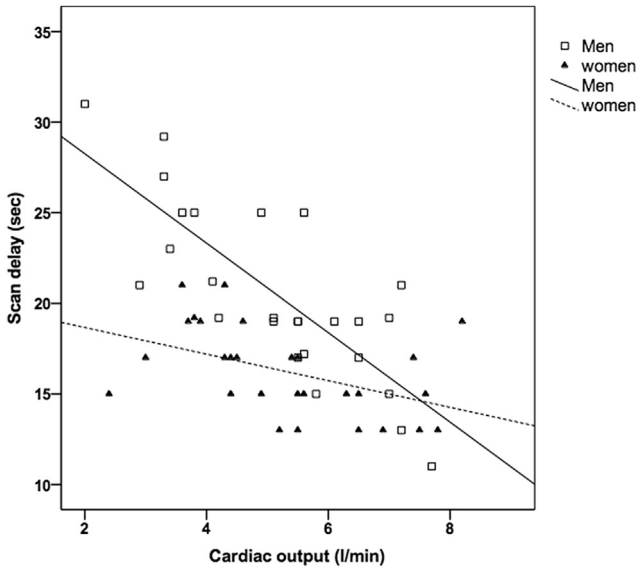

Figure 3 Scatter plot of scan delay versus CO showing a significant negative association between CO and delay for men (β= −2.4, 95% CI: −3.2 and −1.6, $p<0.001$; solid regression line) and a significant negative association between CO and delay for women (β= −0.97, 95% CI: −1.56 and −0.37, $p<0.003$; dotted regression line).

compared to the association of CO and scan delay when gender is not taken into account (β: −1.6, 95% CI: −2.3 and −1.0, $p<0.001$). For women the association between CO and scan delay was less (β: −0.97, 95% CI: −1.56 and −0.37, $p=0.003$).

BP

A significant interaction between BP and scan delay was found in the analyses ($p=0.017$; Fig 4). In patients with a normal BP, the influence on the association between CO and scan delay was less (β: −1.3, 95% CI: −2.0 and −0.6, $p=0.001$) compared to the association of CO and scan delay when BP is not taken into account (β: −1.6, 95% CI: −2.3 and −1.0, $p<0.001$). In patients with a high BP, the association between CO and scan delay increases (β: −3.5, 95% CI: −4.8 and −2.1, $p=0.001$; Fig 4).

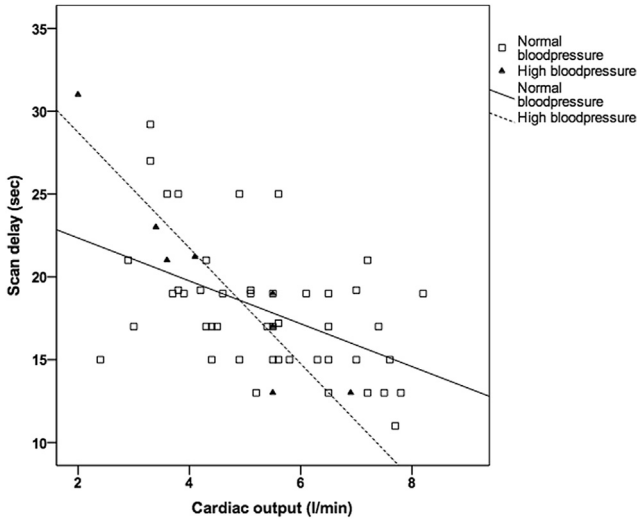

Figure 4 Scatter plot of scan delay versus CO showing a significant negative association between CO and delay for patients with a normal BP (β= −1.3, 95% CI: −2.0 and −0.6, $p=0.001$; solid regression line) and a significant negative association between CO and delay for patients with a high BP (β= −3.5, 95% CI: −4.8 and −2.1, $p=0.001$; dotted regression line).

Discussion

Bae *et al.*[5] demonstrated that the peak of contrast enhancement after the use of a CM bolus is highly correlated with and linearly proportional to the reduction in patient's CO. Mahnken *et al.*[12] reported a high correlation ($r = 0.87$) between the CO determined from test bolus analysis and the CO determined from geometric analysis of retrospectively gated MSCT data. The relation between the CO, measured non-invasively with a finger-cuff measurement, and the scan delay extracted from a test bolus has to the authors' knowledge not been investigated. Therefore, the aim of this study was to investigate the association between CO, as measured using the Nexfin monitor, and scan delay, as extracted from a test bolus injection protocol. The results showed a significant negative association between the CO and scan delay.

Patient weight appeared to be a confounder in the relation between CO and scan delay; gender and BP were effect modifiers. These parameters should also be incorporated into the regression formula when this non-invasive finger-cuff measurement is used to determine the scan delay; however, the prediction interval (Table 2) of the regression formula resulting from the present study is too large to implement in clinical practice. To compute a more reliable regression formula for the scan delay with the use of the Nexfin monitor, the study should be repeated in a larger cohort.

CO

CO, or cardiovascular circulation time, is the most important patient-related factor that affects contrast enhancement timing.[5] As CO is reduced, the circulation of CM slows, resulting in delayed CM bolus arrival and delayed peak enhancement. In case of reduced CO, the CM propagates slowly in the circulation, resulting in higher and prolonged enhancement.[2] To account for variations in the CO among patients, it is important to individualise the scan delay to the CO of the patient. Scan delay can be individualised by using a test bolus or a bolus-tracking protocol.

Test bolus

With the use of a test bolus injection protocol, the individual circulation time can be determined, and CT acquisition can start at the peak of contrast enhancement. As the time–enhancement curve after a test bolus injection contains the cardiac system response, a test bolus examination is likely to hold quantitative information on cardiac function as well.[12] With the use of a test bolus injection protocol,

the amount of CM in a CTA of the abdominal aorta can be reduced with 50%, without compromising image quality[3]; however, the use of a test bolus injection introduces an additional 10–20 ml of CM to determine the peak of contrast enhancement and additional radiation dose (approximately 0.5 mSv). By replacing the test bolus injection with a non-invasive finger-cuff measurement, these additional risks could potentially be avoided.

Nexfin

The Nexfin monitor uses a pulse contour method (Nexfin CO-trek) to employ non-invasive finger arterial pressure. This method uses the pulsatile systolic area as an input to algorithm that incorporates patient specific aortic vascular characteristics to calculate beat-to-beat stroke volume (SV) and cardiac output (CO). A database with intra-arterial and non-invasive finger arterial pressures, as well as thermodilution estimates of CO, served as a learning set.[6] Specific patient characteristics as age, gender, body weight, and height are used as input variables; however, weight appeared to be a confounder in the association between CO and scan delay, and gender and BP were effect modifiers in the present study. Therefore, the output of the Nexfin monitor should be corrected for these patient characteristics.

Alternative techniques that can measure the CO non-invasively are scarce. Transthoracic echocardiography can obtain the CO; however, this technique is time-consuming and beat-to-beat monitoring is not possible.[7] Oesophageal Doppler monitoring uses a probe inserted in the oesophagus to measure the CO continuously.[13] This technique can only be applied for continuous haemodynamic monitoring in sedated and mechanically ventilated patients, which applies for transoesophageal echocardiography as well. An advantage of use of the Nexfin monitor is that the finger cuff can be mounted quickly, and provides its first CO estimate usually within 1 minute with a capability to track changes in CO.[6]

With the injection of CM, patients often feel a warm sensation; this can influence the CO of the patient. Bogert *et al.*[6] showed that the Nexfin monitor can detect even the smallest changes in thermodilution CO, and therefore, can be used even when the CO changes after CM is introduced to the patient.

Limitations

The present study had several limitations. First, a relatively small number of patients were included; therefore, the regression formulas for the confounders were not shown because the numbers of patients in these subgroups were too small to be reliable. Second, with this feasibility study, the Nexfin monitor was used during the test bolus injection to measure the CO of patients and to determine the association between CO and scan delay. The accuracy of the resulting regression formula was not investigated in a clinical setting. Therefore, the resulting regression formula should be evaluated in a second cohort to investigate the accuracy of the formula. Third, the patients included in the study were haemodynamically stable, and therefore, the measured changes in CO were relatively small. Therefore, the performance of the Nexfin monitor during large changes in CO could not be assessed.

In conclusion, there is a negative and significant association between the non-invasive CO measurement and the CT scan delay. Weight appeared to be a confounder in this relation and gender and BP were effect modifiers; however, to validate these findings, a larger cohort study is needed to investigate whether the non-invasively determined scan delay is as accurate as the use of a test bolus.

Acknowledgements

The authors gratefully thank B. Ketelaars, L. Klein Velderman-Arons, and K. Blom, CT radiographers, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands, and Elleke Geertsen, Evelien Maes, and Lonneke van der Laan for their contribution to this manuscript.

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