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Research paper

Quantification of myocardial blood flow using dynamic myocardial CT perfusion compared with ^{82}Rb PET

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ABSTRACT

Purpose: Absolute measures of myocardial blood flow (MBF) obtained with dynamic myocardial CT perfusion (DM-CTP) are underestimated when compared with reference standards. This is to some extent explained by incomplete extraction of iodinated contrast agent (iCA) to the myocardial tissue. We aimed to establish an extraction function for iCA, use the function to calculate MBF_{CT} and to compare this with MBF measured with ^{82}Rb positron emission tomography (PET).

Materials and methods: Healthy individuals without coronary artery disease (CAD) were examined with ^{82}Rb PET and DM-CTP. The factors α and β of the generalized Renkin-Crone model were estimated using a non-linear least squares model. The factors providing the best fit for the data were subsequently used to calculate MBF_{CT}.

Results: Of consecutive 91 individuals examined, 79 were eligible for analysis. The factors α and β providing the best fit of the nonlinear least-squares model to the data were $\alpha = 0.614$ and $\beta = 0.218$ (R-squared = 0.81). Conversion of the CT inflow parameter (K1) values using the derived extraction function resulted in a significant correlation between MBF measured during stress using CT and PET ($P = 0.039$).

Conclusion: In healthy individuals, flow estimates obtained with dynamic myocardial CT perfusion during stress were, after conversion to MBF using the extraction of iodinated CT contrast agent, correlated with absolute MBF quantified with ^{82}Rb PET.

1. Introduction

Coronary computed tomography angiography (CCTA) has become a mainstay of coronary artery disease (CAD) evaluation and is now recommended as the first-line test for chronic coronary syndromes in clinical guidelines.[1–3] However, symptomatic myocardial ischemia leading to ischemic heart disease (IHD) can also exist in absence of obstructive CAD and can be caused by other structural and functional alterations such as microvascular dysfunction. Therefore, methods integrating evaluation of myocardial perfusion are valuable when selecting patients with suspected IHD who may benefit from treatment.[4,5]

Impaired myocardial perfusion resulting in ischemia can be quantified objectively as myocardial blood flow (MBF). The gold standard for animal experimental estimation of MBF is microspheres and for non-experimental use, positron emission tomography (PET) is established as the clinical gold standard.

Nevertheless, other imaging modalities such as echocardiography, single photon emission computed tomography, magnetic resonance imaging and cardiac CT are also capable of estimating both relative distribution of flow and absolute MBF.[5] Among these, dynamic myocardial CT perfusion (DM-CTP) has emerged as a method that in combination with CCTA can provide anatomic and functional evaluation using a single modality.[6] The extent of ischemia determined by DM-CTP can be defined using a relative cutoff value, which in general perform better compared with a cutoff based on absolute results.[7]

Nonetheless, precise quantification of absolute MBF may be important, especially in case of potential three-vessel disease or suspected microvascular dysfunction.[8] Quantification of MBF using DM-CTP is

Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; DM-CTP, dynamic myocardial CT perfusion; iCA, iodinated contrast agent; MBF, myocardial blood flow; PET, positron emission tomography.

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accomplished by the acquisition of multiple images as blood mixed with contrast moves through the myocardium.[9]

Some of the most recent larger DM-CTP accuracy studies have reported absolute MBF values which were substantially lower than the results reported using microspheres and ^{15}O PET.[10–13] It has been suggested that "MBF" calculated as the ratio between the maximum slope of the fit myocardial curve and the peak arterial input function is likely to be computing the inflow rate constant K1 and not true MBF.[14] K1 describes the inflow of tracer from capillaries to tissue and in order to convert the inflow rate to MBF, the extraction of iodinated contrast agent (iCA) is required. The extraction rate describes the proportion of tracer in the capillary blood which is extracted from the blood to the myocardial tissue. Iodinated contrast agent, as well as other small molecules used as tracers, display a distinct roll-off phenomenon where extraction decrease with increasing flow. To account for the incomplete and nonlinear extraction of tracer, an extraction function E(MBF) is needed to convert K1 to MBF.

The present study aimed to establish a relation between flow and extraction of CT iCA in healthy individuals without cardiovascular risk factors and with CCTA verified absence of any CAD. In addition, we aimed to use the derived extraction function to calculate MBF_{CT} and to compare this with MBF measured with ^{82}Rb PET.

2. Methods

2.1. Study population and procedures

This study (The DYNAMITE-PILOT study) was a prospective, single-center observational study performed from October 2020 to December 2021. The study was conducted according to the Declaration of Helsinki II and was approved by The Danish Committee on Health Research Ethics (protocol number H-19043153). Oral and written consent was obtained from all participants. Participants in the DYNAMITE-PILOT study were recruited from the ongoing Copenhagen General Population CT study, in which individuals from the Greater Copenhagen Area are undergoing a research protocol consisting of a non-contrast and a contrast Cardiac CT.[15] Individuals with a calcium score of zero, a normal CCTA and age >45 years were eligible for inclusion in the DYNAMITE-PILOT study.

Specific exclusion criteria of the DYNAMITE-PILOT study included: 1) BMI >35, 2) diabetes, 3) hypertension, 4) hypercholesterolemia, 5) moderate or heavy smoking (>20 pack years), 6) inability to receive study information, 7) bronchospastic lung disease (COPD or asthma), and 8) pregnancy or active breastfeeding.

Participants were assigned for two separate study procedures according to radiation safety constraints. Participants either underwent ^{82}Rb PET (rest and stress) and DM-CTP examination during adenosine stress (*PET and DM-CTP* group), or DM-CTP at rest and during stress (*DM-CTP only* group). Paired flow measures were thus obtained for stress ^{82}Rb PET and stress DM-CTP whereas no paired rest flow measures were acquired.

Both paired results during stress and the unpaired results from examinations at rest were included in the derivation of the extraction function for iCA. The extraction as a function of MBF, E(MBF) was applied to the DM-CTP flow measures to obtain MBF_{CT}, which were then compared with MBF_{PET}.

2.2. DM-CTP image acquisition

Image acquisition was performed using a 320 detector row CT scanner (Aquilion ONE/PRISM Edition, Canon Medical, Otawara, Japan). Participants were instructed to strictly avoid caffeine 16 h prior to examination. Two intravenous lines were inserted, 12-lead ECG was obtained, and oral Beta blockers were administered to participants with a pre-examination heart rate above 65. An individualized contrast volume based on estimated body water was injected at a flow rate of 6 mL/s. Iodinated contrast agent with an iodine content of 350 mg I/ml and a molecular size of 1.2 nm was used (Omnipaque (Iohexol), GE Healthcare, Oslo, Norway).

After a delay of 6 s, low-dose prospective acquisitions were performed at every other heartbeat for 30 consecutive seconds covering the base of the heart to the apex.[16] Tube voltage was 80 kV and tube current was fixed at 300 mA. The scan range was 120 mm covering the entire left ventricle for each rotation, the gantry rotation time was 275 ms and detector collimation was 0.5 mm × 320. Dynamic myocardial CT perfusion was performed as an electrocardiography-triggered prospective target scan acquired at 77–87% of the RR interval. When heart rates above 70 were observed, the scan time was reduced to 25 s to reduce radiation dose.

Adenosine (0.14 mg/kg/min) was used to induce myocardial hyperemia and the stress acquisitions were initiated 3 min after starting the infusion pump. Blood pressure and heart rate was recorded before and 2 min after initiating the infusion of adenosine. The rate pressure product (RPP) was calculated as the product of heart rate and systolic blood pressure. The RPP was calculated for all DM-CTP and PET studies at rest and during stress.

In the *DM-CTP only* group, the stress scan was preceded by an examination at rest performed according to the same scan protocol as the stress. In this group, a wait of 15 min between the first and the second injection of iCA was ensured.

2.3. DM-CTP evaluation and quantification of myocardial blood flow

For the evaluation of rest and stress DM-CTP a low motion phase was determined by an automatic raw data analysis tool (phase eXact, Canon Medical Systems Corporation). Images were reconstructed at 1-mm slice thickness using Iterative dose reduction (Adaptive Iterative Dose Reduction (AIDR) 3D) and a kernel (FC03) with beam hardening correction. Before evaluation, all acquisitions were corrected for breathing related displacement using a non-rigid body registration algorithm. Also, a four-dimensional noise reduction filter (4D similarity filter) was applied.

Interpretation of the image-data and calculation of MBF was performed on a workstation using dedicated software (Vitrea research, version 7.11, Vital Images, a Canon group company, Minnetonka, MN). The semi-automated software set the axis of the left ventricle, identified the contours of the myocardium, and placed a region of interest in the ascending aorta used to obtain the arterial input function. Manual augmentation of the contours was applied when necessary. The left ventricular myocardial tissue was subdivided into 16 segments (excluding the apical cap) according to the American Heart Association myocardial segmentation model. The 16 segments were divided into a total of 864 subsegments. The MBF_{CT} was calculated according to the method described below for every subsegment.[17]

2.4. Quantification of myocardial blood flow

2.4.1. Signal and concentration of contrast

The CT signal is measured in Hounsfield units (HU) and represents the combination of attenuation due to baseline attenuation without contrast and attenuation due to iCA.

$$HU_{measured}(t) = HU_{baseline} + HU_{contrast}(t)$$

Baseline attenuation was measured at the first acquisition before any new contrast had entered and was subtracted from all subsequent measurements.

$$HU_{contrast}(t) = HU_{measured} - HU_{baseline}(t)$$

Using CT, there is a specific linear relationship between signal (HU) and iodine concentration (mg I/ml) at a certain tube voltage (kV).

Kikuchi et al. performed a phantom study using 80 kV and found the following relationship that was adapted in this study.[18]

$$C_{contrast}(t) = \frac{HU_{contrast}(t)}{47.9}$$

2.4.2. Modeling and quantifying flow rates

The flow kinetics within the myocardium were described using a single tissue (two compartment) model developed by Kety and Schmidt together with its assumptions.[19] This is given by the differential equation:

$$\frac{dC_t(t)}{dt} = K_1 * C_a(t) - k_2 * C_t(t)$$

The derivative of the tissue concentration $C_t(t)$ describes the change in the tissue concentration over time. This is determined by the flow into the tissue (the inflow rate constant K_1 multiplied by the concentration of contrast in the arterial blood at the site of extraction (capillaries) at time t) subtracted by the outflow from the tissue (the outflow rate constant k_2 multiplied by the concentration of contrast in the tissue at time t).

K_1 and k_2 were estimated by the non-linear least-squares method where values of K_1 and k_2 were initially assumed. Then optimizations were performed to minimize the least squares error between the result on the right side of the equation and the slope of the tissue curve for all instances of t (left side).

2.4.3. Calculation of myocardial blood flow

Only a fraction of the contrast flowing through the capillaries is extracted to the extravascular compartment.[20] In order to quantitate perfusion, the estimated K1 must therefore be divided by the extraction fraction (E) in order to quantitate perfusion.

$$MBF = \frac{K1}{E} \tag{1}$$

The extraction fraction is defined by an extraction function that is unique for a particular tracer. It is a function of MBF and is dependent on the product of permeability (P) and surface area (S). The permeability-surface area product (PS) describes the flow of molecules through the capillary membranes in a certain volume of tissue. The relation is described by the Renkin-Crone model.[21,22]

$$E(MBF) = 1 - e^{-\frac{PS}{MBF}} \tag{2}$$

This model is consistent with the observation that tracer extraction typically decreases with flow, despite the PS product increasing due to capillary recruitment.[23] The PS function is typically presented on the following form

$$PS = \alpha * MBF + \beta \tag{3}$$

By combining equations (2) and (3), the extraction function can be expressed as

$$E(MBF) = 1 - e^{-\frac{\alpha * MBF + \beta}{MBF}} = 1 - e^{-\alpha - \frac{\beta}{MBF}} = 1 - e^{-\alpha} * e^{-\frac{\beta}{MBF}} \tag{4}$$

Substituting $e^{-\alpha}$ with a

$$E(MBF) = 1 - a * e^{-\frac{\beta}{MBF}} \tag{5}$$

This is inserted instead of E in equation (1) and K1 can be defined by the following expression

$$K1 = \left(1 - a * e^{-\frac{\beta}{MBF}}\right) * MBF \tag{6}$$

The two extraction fraction parameters a and β were estimated for iCA as described in section 2.6. Then, Equations (1) and (5) were combined and MBF_{CT} values were quantified.

$$MBF_{CT} = \frac{K1}{1 - a * e^{-\frac{\beta}{MBF}}} \tag{7}$$

The myocardial flow reserve (MFR) was calculated as the ratio between the MBF during stress and at rest

$$MFR = \frac{MBF_{Stress}}{MBF_{Rest}}$$

2.5. PET image acquisition, evaluation and quantification of MBF

Perfusion imaging with DM-CTP and ^{82}Rb PET was separated by a minimum of 48 h. All patients were asked to abstain from caffeine 12 h prior to imaging. PET myocardial perfusion imaging was performed during rest and stress conditions in a single session. For each condition, participants received 1110 MBq (±10%) ^{82}Rb supplied from a CardioGen-82 Sr-82/Rb-82 generator manufactured for Bracco (Bracco Diagnostics Inc., Princeton, NJ).

Rest and stress images were acquired electrocardiography-triggered for 6 min from the start of the ^{82}Rb infusion on a Siemens Biograph mCT/PET 128-slice scanner (Siemens Healthcare, Knoxville, TN, USA). Adenosine (0.14 mg/kg/min) was used to induce myocardial hyperemia for 6 min, and the ^{82}Rb infusion was initiated 2.5 min after starting the infusion of adenosine.[24]

The 6 min long PET acquisitions were reconstructed into dynamic image-series consisting of 18 frames (1 × 10s, 8 × 5s, 3 × 10s, 2 × 20s, 4 × 60s) using an iterative 3D ordered subset expectation maximization model (2 iterations and 21 subsets) with corrections for time-of-flight and point-spread function. All data were smoothened using a 6.5-mm Gaussian post-filtering.

The left ventricular myocardial tissue was subdivided into 17 segments.[17] No manual adjustments were made. Pre-study evaluations showed inclusion of extramyocardial structures in the basal segments and segments 1–6 were therefore excluded from analysis. In addition, segment 17 was also excluded from the analysis to comply with the DM-CTP evaluation protocol. The ^{82}Rb PET MBF values (MBF_{PET}) were calculated according to the Lortie model using dedicated software (QPET, Cedars-Sinai Medical Center, Los Angeles, California, USA).[25]

2.6. Derivation of extraction function and calculation of MBF

Both flow measures obtained at rest and during stress were used for derivation of the extraction function. Since the rest observations were unpaired, the rest observations were divided in three groups of ten DM-CTP observations in each based on the size of the RPP, which was from the literature expected to be related to MBF at rest.[26] The three groups were matched with the same RPP interval measured at the ^{82}Rb PET rest examination. The mean of the three RPP group values given the weight equivalent to the number of CT observations were utilized as data points for the derivation of the extraction function in addition to the stress results.

The parameters a and β of the generalized Renkin-Crone model in Equation (6) were estimated using a non-linear least squares model. Values of a and β providing the best fit for the data were used to calculate MBF_{CT} by solving Equation (7).

Then, the derived extraction function was applied to the DM-CTP flow measures (K1 at rest and during stress) in order to obtain MBF_{CT} (Equation (7)), which were finally compared with absolute flow quantitated with ^{82}Rb PET (MBF_{PET}).

2.7. Comparison of extraction with existing literature

In order to assess the derived extraction function, the extraction fraction (E) of iCA was calculated for the mean MBF_{CT} at rest and during stress of the present study as well as for theoretical MBF values at rest, MBF = 1 mL/min/g and during stress, 4 = mL/min/g. The current literature was reviewed for research describing the extraction of iodinated contrast from blood to the myocardial tissue. Two clinical and one animal experimental study were identified (Table 1).[18,20,27] Since no experimental data describing the extraction at rest were identified, two studies on the fractional extraction of comparable molecules were included.[28,29] Estimates for parameters a and β acquired from the

Table 1
Extraction (E) of iodinated CT contrast agent and other small molecules.

	Tracer	E at rest	E at MBF = 1 mL/min/g	E during stress	E at MBF = 4 mL/min/g
Experimental estimation					
Canty et al., 1991	CT CA (Ioversol)			0.33 ± 0.02	
Svendsen et al., 1991	Small molecules[a]	0.46 ± 0.04			
Svendsen et al., 1992	^{99m}Tc-DTPA	0.55 ± 0.09			
Reference standard estimation					
Kikuchi et al., 2014	CT CA (Iohexol)		0.73		0.33
Takafuji et al., 2021	CT CA (iodinated)		0.81		0.39

All studies are included in the reference list. E = 1 and 4 are approximate reference flows at rest and during stress for healthy individuals. Studies investigating extraction of CT CA are highlighted in grey.
CA: contrast agent; DTPA: diethylenetriamine pentaacetate; EDTA: ethylenediaminetetraacetic acid; MBF: myocardial blood flow.
[a] Small hydrophilic molecules with comparable size and properties as iodinated CT contrast agent. MBF at rest and stress are presented ± 1SD. For MBF = 1 and 4, no SD's are available since the value is derived from the extraction function.

literature were used to generate extraction functions, on the generalized Renkin Crone formula, for graphical comparison.

2.8. Statistical analysis

Using descriptive statistics, the continuous variables are expressed as mean ± SD and the categorical data are expressed as frequency (percentage). The Mann-Whitney *U* test (Wilcoxon rank-sum test) was used for comparison of non-parametric data and the students *t*-test was used to asses differences in parametric data across groups. Sex and family history of cardiovascular disease are expressed as frequency (percentage) and the Fisher's exact test was used to assess differences in proportion. The relationship between continuous variables was assessed using the Pearson correlation coefficient. *P*-values of <0.05 were considered significant. All statistical analyses were performed using R statistical package, version 3.6.1 (R Foundation for Statistical Computing).

3. Results

Due to the COVID-19 pandemic, the planned enrollment of 100 participants were hindered and a total of 91 healthy individuals were enrolled and underwent either rest and stress ^{82}Rb PET and stress DM-CTP (*PET and DM-CTP* group, $n = 57$) or DM-CTP only including both rest and stress (*DM-CTP only*, $n = 34$). Of the consecutive 91 participants examined, 79 were eligible for analysis (Fig. 1). Twelve participants were excluded due to technical failure ($n = 4$), structural heart disease discovered after inclusion ($n = 3$), PET examination not performed ($n = 3$), CA extravasation ($n = 1$) and discomfort (severe dizziness) during adenosine ($n = 1$)). There were no significant differences in sex, age, BMI or prior smoking between the *PET and DM-CTP* and *DM-CTP only* groups (Table 2). Participants in the *PET and DM-CTP* group had a median time between examinations of 14 days (range; 2–91 days).

3.1. Hemodynamics

A significant increase in heart rate as well as RPP during stress conditions in the *PET and DM-CTP* group was observed for both PET (heart rate; 64 vs. 80 bpm, $P < 0.01$ and RPP; 7485 vs. 9405 bpm · mmHg, $P < 0.01$) and DM-CTP (heart rate; 58 vs. 75 bpm, $P < 0.01$ and RPP; 7624 vs. 9591 bpm · mmHg, $P < 0.01$). No significant differences in the RPP were observed between the CT (7624 ± 1363 at rest and 9591 ± 2446 during stress) and PET examination (7485 ± 1558 bpm · mmHg at rest and

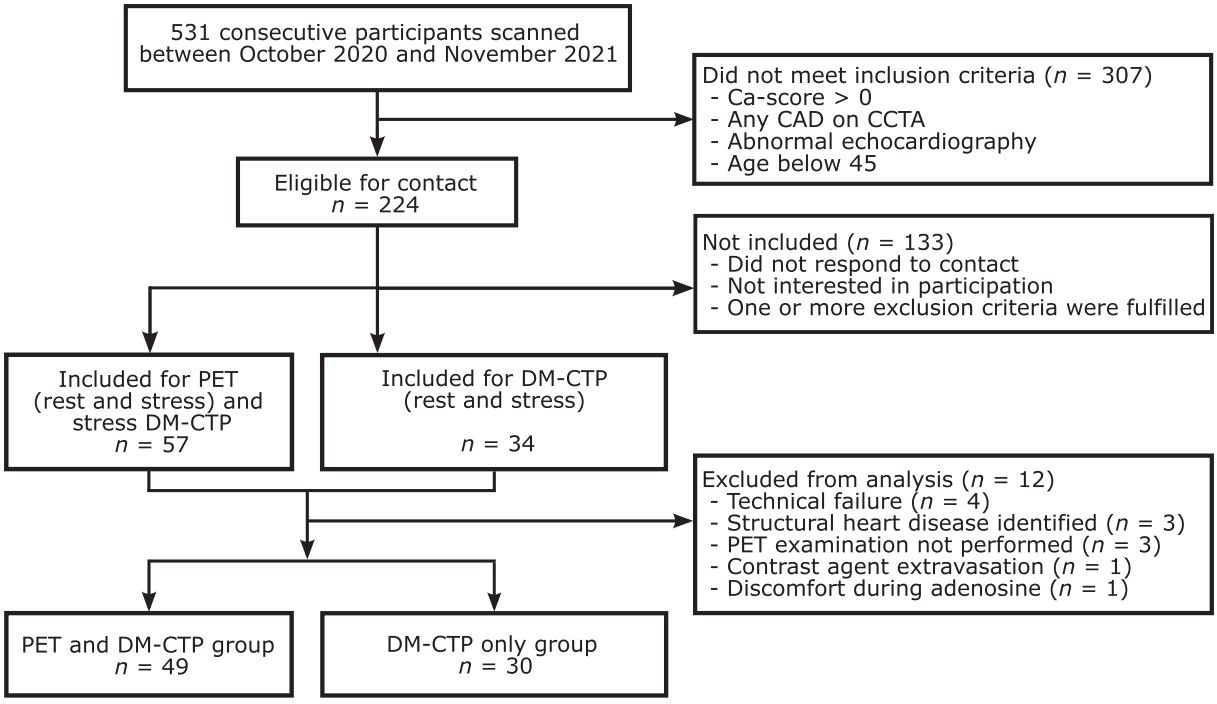

Fig. 1. Participant flowchart. DM-CTP = dynamic myocardial CT perfusion, CAD = coronary artery disease, CCTA = coronary CT angiography, PET = positron emission tomography.

Table 2
Characteristics of the study population.

	PET and DM-CTP	DM-CTP only	*P*-value
Baseline characteristics			
N	49	30	
Female	27 (55)	16 (53)	1.00
Age (years)	56.29 ± 8.56	57.27 ± 8.56	0.60
BMI (kg/m2)	24.44 ± 3.51	23.86 ± 2.63	0.40
Smoking (pack-years)	2.55 ± 4.72	3.70 ± 4.70	0.76
Family history of CVD	6 (12)	1 (3)	0.24

Data are presented as counts (percentage) or mean ± standard deviation.
CCTA: coronary CT angiography; CVD: Cardiovascular disease.

9405 ± 1989 bpm · mmHg during stress). Between procedure reproducibility of the RPP during stress for all subjects of the PET and DM-CTP group was high (r = 0.98) (Fig. 2).

3.2. Extraction function for iodinated contrast

In Fig. 3, the K1 estimates obtained with DM-CTP are plotted against the absolute MBF obtained with ^{82}Rb PET. K1 was 0.48 ± 0.17 mL/min/g at rest and 1.50 ± 0.45 mL/min/g during stress. The factors a and β providing the best fit of the nonlinear least-squares model (see equation (6)) to the data was $a = 0.61$ and $\beta = 0.22$ (R-squared = 0.81).

The resulting extraction function $E = 1–0.61 \times e^{-0.22/MBF}$ lead to a mean extraction fraction at rest of 0.52 ± 0.05 and 0.43 ± 0.03 during stress. The extraction function derived in the present study is plotted in Fig. 4 along with the extraction functions derived by the two clinical studies by Kikuchi et al. and Takafuji et al.[18,27]

3.3. Estimates of myocardial blood flow using DM-CTP

A comparison of MBF estimated with ^{82}Rb PET and MBF_{CT} obtained by conversion of DM-CTP K1 values to MBF_{CT}, using the derived extraction function and equation (7), are presented in Fig. 5. A significant correlation between MBF measured during stress using CT and PET was found ($P = 0.039$).

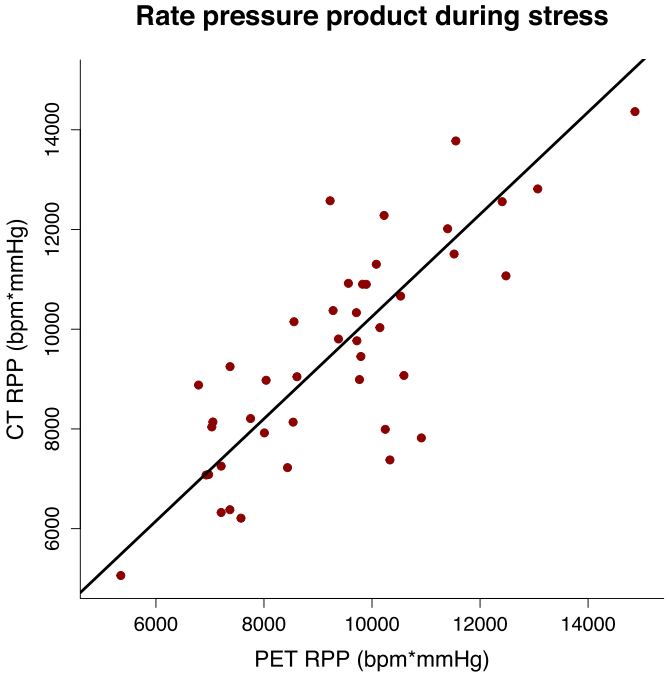

Fig. 2. Rate pressure product at ^{82}Rb PET and DM-CTP. PET = positron emission tomography, RPP = rate pressure product.

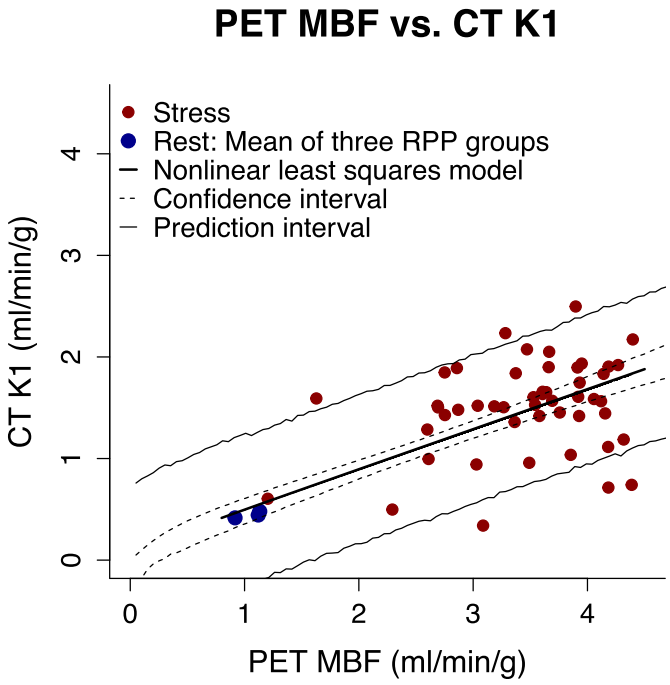

Fig. 3. K1 obtained with DM-CTP and MBF obtained with ^{82}Rb PET. Solid black line represents the nonlinear least squares model with equation $K1 = (1–0.61 \times e^{-0.22/MBF}) \times MBF$ with best fit to the data (a = 0.614 and β = 0.218).

A group comparison of MBF measured with the two modalities is included in the supplementary material.

4. Discussion

In the present study, an expression determining extraction as a function of MBF based on the generalized Renkin Crone model was established by using ^{82}Rb PET as the reference standard; $E = 1–0.61 \times e^{-0.22/MBF}$.

The extraction of a tracer can be estimated indirectly, as shown in the present study, by using a reference representing "true" MBF but can also be estimated by direct measurement of arterial and venous concentration, although this is difficult to achieve in humans.

Direct experimental estimation of extraction of iCA has been undertaken by Canty et al. in a very elegant study.[20] They compared the CT myocardial signal of a conventional nonionic CA (ioversol) to a particulate emulsion (ethiodol) that remained in the vascular space in closed-chest dogs during pharmacological vasodilation and found an extraction fraction of 0.33 ± 0.02. The study was not performed at rest. However, they also reported extraction of 50 ± 3% in areas supplied by vessels with induced stenosis, which might be somewhat comparable to the resting condition since the hyperemic response is blunted or absent in areas with ischemia during stress.

The indirect method has been utilized to establish the extraction of iCA by Kikuchi et al. and Takafuji et al. who determined the relation between extraction of iCA and MBF using the current non-invasive gold standard ^{15}O PET and found $E = 1–0.90 \times e^{-1.20/MBF}$ and $E = 1–0.90 \times e^{-1.54/MBF}$ respectively (Fig. 4-A).[18,27] Characteristics separating these studies from the present are sample size (N = 12 and N = 17 vs. 49 matched and 30 unmatched individuals), CAD status (absence of significant CAD and known or suspected CAD vs. CCTA verified absence of any CAD in our study) and finally the reference method. These differences complicate the direct comparison. However, inspection of the extraction functions of the two studies reveals supraphysiological extraction values at MBF <1.5 mL/min/g when compared with experimental data. On the other hand, it seems that the extraction functions derived by Kikuchi et al. and Takafuji et al. reflect the experimental data better at MBF >3.0 mL/min/g compared with the extraction function of the present study.

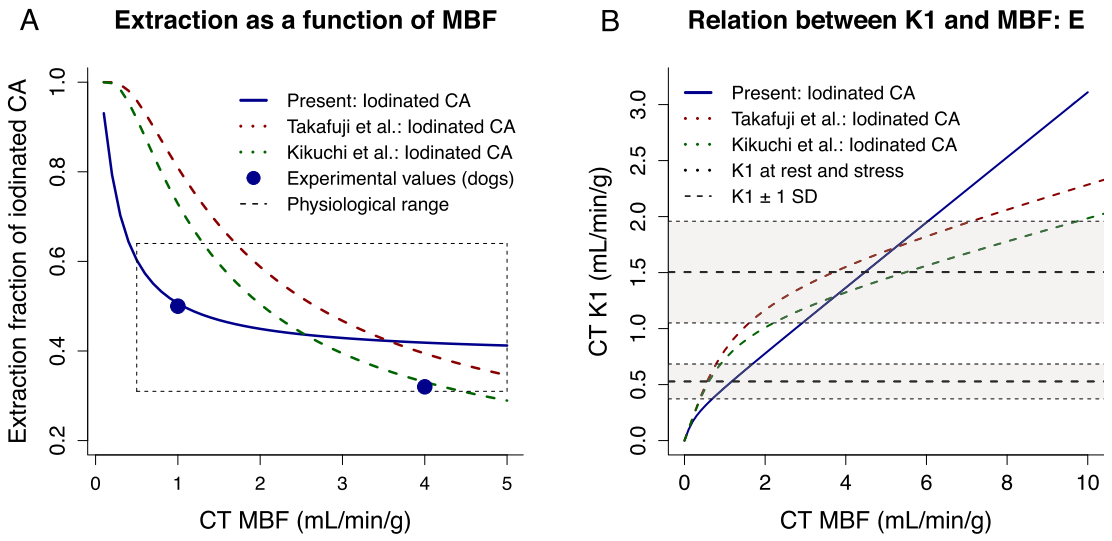

Fig. 4. Two representations of the extraction function. A, Extraction fraction as a function of MBF. MBF = 0.5 to 5.0 and extraction fraction of 0.31–0.64 represent physiological range. Blue dots represent extraction fraction estimates obtained by animal experiments at rest and during stress which are presented in Table 1 (Rest = 0.5 and stress = 0.33). B, Relation between K1 and MBF. Grey zones represent DM-CTP K1 ± one standard deviation obtained in the current study at rest and during stress. MBF = myocardial blood flow.

The consensus of the present and the two other clinical studies is that extraction of iCA to the myocardial tissue during first pass is incomplete. Assuming complete extraction results in MBF_{CT} equal to K1 which would cause significant underestimation of MBF_{CT}. In addition, the extraction fraction of iCA decrease with increasing flow and using a constant for conversion is therefore not optimal and would potentially result in overestimation of resting and underestimation of hyperemic flow.

In the present study, we found a significant correlation between MBF measured during stress using CT and PET. This adds to the growing body of evidence regarding the accuracy of myocardial blood flow estimation from DM-CTP compared with PET.[18,27,30] However, when inspecting the individual observations, results are scattered. A contributing factor could be the discrepancy between the blood flow kinetics visualized using the two modalities. Because of a short injection time of the CT tracer (5–10 s), a high temporal resolution and an acquisition time of 30 s, only the first pass is visualized. In comparison ^{82}Rb is injected much slower, the temporal resolution is lower and the total acquisition time is 6 min. The kinetics visualized using PET are therefore different compared with DM-CTP.

In addition, scattered results, represented by large distance to the best fit to the data, are also seen when comparisons within the same modality are undertaken. One example of similar scattered results is the study by Lortie et al. which compares ^{82}Rb PET with ^{13}N-ammonia PET.[25] Nevertheless, the general impression is that the results obtained with PET is reproduced using DM-CTP, which is reflected by the significant correlation.

4.1. Limitations

The primary limitation of this study is the single center, single scanner, single perfusion CT software and single CA injection protocol setup. Apart from the injection protocol, the extraction is not dependent on these factors. Nevertheless, when using the indirect extraction function derivation method utilized in the present study, these factors will impact the result. In addition, the estimated extraction function is based on MBF obtained with the chosen reference standard which in this study was ^{82}Rb PET. Despite the limited clinical implementation, ^{15}O PET is still considered the gold standard for quantification. Another important limitation of this study is the lack of paired ^{82}Rb PET and DM-CTP examinations at rest that would have improved the total number of paired observations and most likely, robustness of the results.

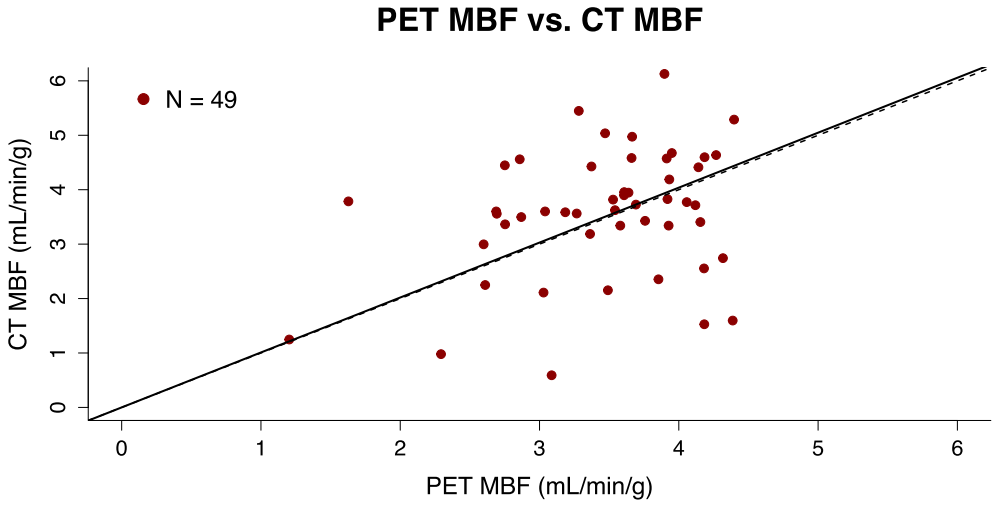

Fig. 5. Myocardial blood flow during stress evaluated with dynamic myocardial CT perfusion and ^{82}Rb PET. A significant correlation between MBF measured during stress using CT and PET was found (P = 0.039). Dotted line represents identity line and solid line represents best fit to the data. Since no paired data w obtained at rest, the regression line was forced through the origin, which is physiologically rational. Slope = 1.01 and R^2 = 0.90. R-squared should be interpreted with caution due to the exclusion of the intercept in the best fit. MBF = myocardial blood flow.

4.2. Clinical implications of this study

This study aims to increase the awareness that the inflow rate (K1) is significantly different from MBF_{CT} and that an extraction function is necessary for absolute quantification of MBF_{CT} if comparison of absolute numbers with other modalities is intended (Fig. 4-B).

Since quantification depends on parameters mentioned in the limitations, the extraction function is ideally evaluated before undertaking clinical DM-CTP using site-specific set-up. However, this approach is not feasible for most sites and as an alternative, the extraction function presented in this study can be adopted and tedious work bypassed. This especially applies when similar set-up is utilized.

Because a sampling rate of one acquisition for every second heartbeat was selected in the present study, the scan protocol is also applicable to dual-source CT scanners (that must alternate table position due to limited z-axis range) which has been employed in most of the previous DM-CTP studies. Before implementation, use of the presented extraction function should undergo clinical validation.

5. Conclusions

In this study, the first pass extraction of iodinated CT contrast agent to the myocardial tissue as a function of flow was defined in a cohort with coronary CT angiography verified absence of coronary artery disease. Flow estimates obtained with dynamic myocardial CT perfusion during stress were, after conversion to myocardial blood flow using the derived extraction function, correlated with absolute myocardial blood flow quantified with ^{82}Rb positron emission tomography. Experimental estimation of the extraction of iodinated contrast agent in humans over a range of myocardial blood flows, which is unaffected by scanner, protocol and software, is warranted but difficult to achieve.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2023.03.007.

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