Article

Fractional Flow Reserve Derived from Computer Tomography in Asymptomatic Patients with Type 2 Diabetes and Albuminuria without Significant Coronary Artery Stenosis—A Surrogate for Coronary Microvascular Dysfunction?

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Abstract: Background: Type 2 diabetes mellitus (T2D) patients with albuminuria have coronary microvascular dysfunction (CMD). Fractional flow reserve assessed by coronary computed tomography angiography (FFRct) is dependent on the structure and function of the microcirculation and is likely influenced by CMD. We aimed to evaluate if asymptomatic patients with T2D who had no significant coronary artery stenosis but had been diagnosed with albuminuria had lower value of nadir FFRct compared to asymptomatic patients with T2D and no albuminuria. Methods and results: This was a cross-sectional study which compared the mean nadir FFRct values in coronary arteries in patients with T2D who had no symptoms of angina. The T2D patients were divided into two groups (albuminuria and no albuminuria) with albuminuria being defined as albumin–creatinine-ratio (ACR) ≥30 milligram per gram. The nadir FFRct values were compared between the two groups for left anterior descendent artery (FFRct-LAD), circumflex artery (FFRct-CX), and right coronary artery (FFRct-RCA) by using a two-sample Wilcoxon rank-sum (Mann–Whitney) test. Ninety-eight patients without albuminuria and 26 patients with albuminuria were included. No significant differences in mean values were detected for FFRct-CX 0.86 ± 0.07 and 0.88 ± 0.0, FFRct-RCA 0.88 ± 0.05 and 0.88 ± 0.07, or for FFRct-LAD 0.82 ± 0.07 and 0.82 ± 0.07 in patients with albuminuria and without albuminuria, respectively. Conclusion: In this observational study, we did not find that FFRct was affected by CMD. Therefore, it is not a surrogate for microvascular dysfunction in asymptomatic T2D patients with albuminuria.

Keywords: type 2 diabetes; albumin–creatinine ratio; coronary microvascular dysfunction; coronary computed tomography angiography; fractional flow reserve

1. Introduction

Patients with Type 2 Diabetes (T2D) have a two- to fourfold increased risk of ischemic heart disease when compared to non-diabetes patients [1,2]. It is known that patients with T2D and diabetic complications such as albuminuria are at increased risk of mortality even without coronary artery calcification [3]. There are many possible explanations for this, such as earlier and more pronounced arterioscleroses [4] or endothelial dysfunction [5,6].

Coronary microvascular disease (CMD) is a result of dysfunction in small coronary arteries that have a diameter of less than 500 µm. This condition can impair both types of diabetes patients [7] and has been shown to be independently associated with cardiac mortality [3]. Albuminuria in diabetes patients is believed to be related to CMD when compared to T2D patients without albuminuria [8,9].

Determining CMD requires invasive measures of quantitative perfusion in coronaries by imaging, measurement of endothelium dysfunction, and visualization of coronary abnormality [10,11]. CMD cannot be identified on a large scale by any known non-invasive
imaging modality and can therefore only be proven indirectly through stress test coronary flow reserve by echocardiography [12], positron emission tomography (PET) [7], or symptoms (i.e., microvascular angina) [13], with PET having been proved the most accurate test.

The literature has shown that impaired myocardial flow reserve for patients with T2D can be determined by Rubidium PET and is closely related to the degree of albuminuria [9]. This has led to a relationship between CMD and albuminuria being suggested [9]. Cardiac and renal microvascular dysfunction in T2D is also believed to share a similar mechanism [9,14]. The frequency of silent myocardial ischemia determined by myocardial stress perfusion imaging has been shown to be 11 times higher in patients with T2D with albuminuria compared to T2D patients without albuminuria [15], and CMD could be the main reason.

Fractional flow reserve assessed by coronary computed tomography angiography (FFRct) is a novel non-invasive method which evaluates the functional importance of an anatomical stenosis by coronary computed tomography angiography (CCTA) with values < 0.8 determined for ischemia [16,17]. The exact mechanism of FFRct is based on well-known laws of hydrodynamic physics. One of the basic steps of FFRct is the calculation of epicardial coronary artery resistance (large arteries) during both rest and virtual simulation of hyperemia. When the coronary arteries are “normal”, the FFRct is based on the following three assumptions [18]: (1) Total coronary blood flow at rest is proportional to the oxygen demand of myocardium; (2) Coronary microcirculation has a predictable response to the vasodilator administration; and (3) Resistance of the coronary microcirculation is inversely proportional to the size of the feeding vessel.

The FFRct estimate is thus dependent on the structure and function of microcirculation, which affects diabetic patients with albuminuria. The FFRct can hence be dependent on both stenosis of the epicardial coronaries and CMD.

Our aim was to examine if FFRct is significantly lower in a population of asymptomatic patients with T2D and albuminuria when compared to a group of patients with T2D without albuminuria. We thus investigated if FFRct could be used as a non-invasive surrogate of CMD.

2. Methods

2.1. Study Populations

Our study is a substudy of a single centre study performed at the Cardiovascular Research Unit at Odense University Hospital in Svendborg, Denmark from March 2016 to September 2017. A total of 261 asymptomatic patients older than 18 years with T2D from an outpatient diabetes clinic were examined. All patients signed an informed consent to participate in the original study. Patients were not eligible if they had a history of ischemic heart disease, currently presented with symptoms of angina, were documented as having heart failure, had estimated glomerular filtration below 45 mL/min, or were allergic to iodine contrast.

A detailed health status was recorded for all patients. Blood was drawn for creatinine, glycosylated hemoglobin HbA1c, and lipid profiles. Spot-urine tests were collected from all patients to assess micro and macro-albuminuria. Albuminuria was defined as ACR above 30 milligram/gram in at least 2 independent samples in patients without symptoms of urinary tract infection. Patients receiving one or more antihypertensive drugs were categorized as having hypertension. Patients treated with one or more lipid-lowering drugs were categorized as having hypercholesterolemia.

CCTAs were performed from 2016–2017; 142 of those had FFRct determined.

2.2. CCTA

CCTAs were performed according to SCCT guidelines [19]. Even though patients were asymptomatic, CCTAs were performed to evaluate coronary arteriosclerosis in a cohort of diabetes patients.
Initially, all patients had an unenhanced scan to assess coronary artery calcium which was followed by a CCTA. A 256-slice scanner (Revolution CT scanner from GE Healthcare, Waukesha, WI, USA) with a gantry rotation at 280 ms and a collimation of $256 \times 0.625$ mm was also used. All patients received 7.5 mg of Ivabradin daily for 2 days prior to scanning. All patients with a heart rate (HR) > 60 beats/minute received beta-blockers intravenously on the day of CCTA, and a HR < 65 was considered optimal for good image quality scanning. Sublingual fast acting nitrates were administered by spray 1–2 min before the enhanced scan, and images were obtained by an ECG-gated prospective acquisition in the 75% of the R-R interval with additional padding of 45 milliseconds (ms) to allow additional reconstruction. A total of 60 mL of iodine contrast medium (Visipaque 320 mg/mL) was used.

Tube voltage and current were modulated to the patient’s body size with a tube voltage between 80 and 140 kV and a tube current between 350 and 700 milliamperes according to body mass index. The median radiation dose per scan was 2.01 mSv. All phases were reconstructed and images with superior image quality were selected for analysis.

All images were analyzed by a Level III certified observer who was blinded to patient data. Only major coronary arteries were analyzed. Luminal stenosis of $\geq 50\%$ was considered significant, and the patient was excluded from further analysis.

(Fractional flow reserve assessed by coronary computed tomography angiography.)

2.3. FFRct

FFRct was derived from standard CCTA evaluation. The substudy was conducted half-way through the main study and only 142 consecutive patients were analyzed by FFRct.

Standard CCTA datasets were transmitted anonymously through an encrypted connection to the external Core Laboratory (HeartFlow Inc., Redwood City, CA, USA). Before analyzing the CCTA, the FFRct Core Laboratory applied a second set of quantitative criteria to determine if the image quality was adequate for FFRct analysis, after which the FFRct was performed.

Techniques for the FFRct analysis were performed by HeartFlow Inc and have been previously described in detail by other investigators [18]. In brief, the FFRct model provided computed FFRct values in all vessels of the coronary tree with diameter $\geq 1.8$ mm. The lowest per-vessel FFRct values (nadir FFRct) were reported for FFRct-LAD, FFRct-CX, and FFRct-RCA.

2.4. Statistics

Statistical analyses were performed by STATA IC ver. 14. Continuous variables are presented as mean $\pm$ SD. A two-sample Wilcoxon rank-sum (Mann–Whitney) test was used to compare the means between the 2 groups, and a one-sided Fisher’s exact test was used to compare the proportions between the groups. A 95% confidence interval or standard deviation (sd) is shown.

3. Results

3.1. Study Population

A total of 142 T2D patients had FFRct performed. Eighteen patients were excluded due to non-diagnostic image quality in 10 patients, a stenosis $\geq 50\%$ of the luminal diameter in the coronaries as determined by CCTA in 6 patients, and non-evaluable for FFRct determination in 2 patients, respectively. Figure 1 is a flowchart that shows the selection of patients in the study.
Figure 1. Both groups were primarily male, with 58% in the group with albuminuria being male and 62% in the group without albuminuria being male, respectively. There were no statistically significant differences between groups. Additionally, the risk factor distribution and CCTA parameters were comparable with no significant differences found between the groups. Baseline values are listed in Table 1. Mean CAC score between groups was non-significant, although a broader range was seen in the non-albuminuria group.

Table 1. Baseline characteristics of the non-albuminuria and albuminuria T2D groups.

| Baseline Characteristics                  | Non-Albuminuria (n = 98) | Albuminuria (n = 26) |
|-------------------------------------------|--------------------------|---------------------|
| Sex male n (%)                            | 57 (58)                  | 16 (62)             |
| Age (y) mean ± SD                         | 61.2 ± 9.4               | 61.3 ± 9.1          |
| HbA1C mmol/mol                             | 59 ± 13                  | 62 ± 12             |
| Hypertension n (%)                         | 60 (61)                  | 16 (62)             |
| Urine-albumin-creatinine ratio Mmol/L mean (Cl) | 13.0 (10.5–15.6)        | 104 (63.7–144.6) *  |
| Dyslipidemia n (%)                         | 73 (75)                  | 22 (85)             |
| Active Smoking n (%)                       | 53 (54)                  | 13 (50)             |
| BMI, kg/m² mean ± SD                      | 30 ± 4.4                 | 31 ± 4.5            |
| CCTA Heart rate (beats/min) mean ± SD     | 57 ± 8.1                 | 58 ± 7.4            |
| DLP (mGy * cm) mean (CI)                  | 92.9 (86.1–99.7)         | 99.9 (82.2–117.7)   |
| CAC (Agatston) mean (min–max)             | 293 (0–2722)             | 298 (70–700)        |

Values are presented as mean with corresponding standard deviation (SD) or confidence interval (CI) or numbers (n) and corresponding percentage (%). BMI = Body mass index; CAD = Coronary artery disease; CCTA = Coronary computer tomography angiography; CAC = Coronary artery calcium; DLP = Dose length product. * p < 0.05.
3.2. FFRct

The distribution and mean values for nadir FFRct are shown in Table 2. No differences for FFRct-CX, $0.86 \pm 0.07$ and $0.88 \pm 0.05$, FFRct-LAD $0.82 \pm 0.07$ and $0.82 \pm 0.07$ or FFRct-RCA $0.88 \pm 0.05$ and $0.88 \pm 0.07$ were found when comparing the T2D patients without albuminuria with T2D patients with albuminuria, respectively.

A representative case for CCTA in a patient with T2D for CX, LAD, and RCA is shown in Figure 2a with the corresponding FFRct assessment in Figure 2b.

![Figure 2a and 2b](image)

**Figure 2.** (a) CCTA of CX and corresponding FFRct. FFRct for CX is 0.89. (b) CCTA of LAD and corresponding FFRct. Nadir for FFRct on LAD is 0.80. Arrows showing mixed and soft plaque in CCTA images.

**Table 2.** Comparison of mean fractional flow reserve (FFRct) by computed tomography angiography in all 3 main coronary arteries between the 2 groups.

| FFRct | Non-Albuminuria ($n = 98$) | Albuminuria ($n = 26$) | $p$-Value |
|-------|---------------------------|------------------------|-----------|
| CX    | 0.86 (0.07)               | 0.88 (0.05)            | ns        |
| LAD   | 0.82 (0.07)               | 0.82 (0.07)            | ns        |
| RCA   | 0.88 (0.05)               | 0.88 (0.07)            | ns        |

Values are presented as mean with corresponding standard deviation (SD). ns = No significant differences; FFRct = Fractional flow reserve by computed tomography angiography; CX = Circumflex artery; LAD = Left ascending artery; RCA = Right coronary artery.
4. Discussion

Recent advances in computational fluid dynamics and individual image-based modelling allow calculation of coronary blood flow and pressure from standard CCTA datasets. This permits non-invasive calculation of FFRct and has been proven to be a valuable tool in the clinical setting regarding the assessment of whether the stenosis found by CCTA is with or without hemodynamic significance [20–22]. The final step in the FFRct assessment for a coronary artery with stenosis is simulating a maximal hyperemic effect of adenosine stimulation, which assimilates the reduction in the microvascular resistance downstream of the epicardial coronaries. It has been assumed that the microcirculatory resistance is the same as when coronary arteries have no disease [23]. Nevertheless, in a study by Taylor et al. [23] (which describes the assessment of FFRct in detail), it was observed that a significant limitation for assessment could be patients with microvascular dysfunction as models of adenosine hyperemia, which may overestimate vasodilation and therefore give low FFRct values.

To our knowledge, our study is the first to investigate if FFRct is affected by potential microvascular dysfunction and if the technology could be used as a surrogate for CMD in coronary arteries in T2D patients with albuminuria. Our study was not able to demonstrate this, as no significant difference in mean FFRct values in any of the coronary arteries compared to patients with T2D in relation to having albuminuria was found. Thus, our study could not conclude if FFRct can or cannot detect CMD or whether the accuracy of FFRct is affected by CMD.

There is no practical limitation to performing FFRct on symptomatic patients with theoretically affected microvascular circulation, which was demonstrated in a small study of 16 T2D patients by Eftekhari A et al. [24]. The Eftekhari study found that FFRct performance is independent of the presence of hypertension or T2D in a population of stable CAD patients which was validated by using a machine-learning based CT-FFR software [25]. Accordingly, there should not be technical problems performing FFRct in diabetes patients.

It is well known that different parameters (i.e., betablockers, nitroglycerin, and motion artefacts) affect the performance of FFRct [26]. Likewise, vessel geometry and hemodynamic differences could also influence the FFRct values [27].

In this study, all patients received both nitroglycerin and ivabradine and, eventually, beta blockers according to HR. We excluded participants with low image quality, and HR before CCTA did not vary significantly between the groups. CAC could be an additional factor affecting FFRct although B.Norregard et al. [28] showed no differences in diagnostic accuracy across CAC scores values and CAC scores were similar in both groups.

CMD in T2D patients was shown to be significantly related to albuminuria and determined by ACR [9]. Potier L et al. found a progressively decreased myocardial flow reserve in T2D symptomatic patients with both microalbuminuria and macroalbuminuria when compared to normoalbuminuria and adjusting for confounders. These results were confirmed when Potier et al. analyzed only patients with low levels of coronary calcification. Potier et al. included only patients without coronary stenosis confirmed by an invasive coronary angiography for both patients with microalbuminuria and macroalbuminuria. This was comparable with our patients although our patients were asymptomatic, had a lower pretest probability for coronary artery disease, and theoretically had a lower degree of CMD.

Interestingly, Potier L et al. found no differences for myocardial flow reserve between normoalbuminuric T2D patients and normoalbuminuric non-diabetes patients. This confirmed our choice of having dichotomized our diabetes patients into two groups, which was in accordance with the ACR expecting difference in prevalent CMD.

A study by Scholten et al. [14] examined 60 type-2 diabetes and 30 non-diabetes patients. This study showed a relation of CMD to diabetes but not to albuminuria, even though a trend towards a higher degree of CMD with albuminuria was shown. In a different study, the microcirculation was affected in T2D patients by an increasing wall to
lumen ratio, which narrowed the vessel diameter in small arteries and affecting coronary microvascular flow [12, 29].

In theory, these factors should reduce the maximum hyperemic flow during adenosine and lead to a fall in FFRct values. This was demonstrated by Nahser PJ et al. when an invasive coronary flow measurement with adenosine was performed on a group of 12 T2D patients. A comparison of a matching control group without T2D and coronary stenosis was also performed in this study.

The Nahser study demonstrated a reduced maximal coronary vasodilation and impairment in flow regulation in response to stressors in the T2D patients, both of which are parameters representing signs of CMD. The particular method used is based on invasive measures and is not applicable on a large scale study such as ours. A more applicable non-invasive method to measure microvascular dysfunction could be light-induced arteriolar dilation or heart-induced skin hyperemia, as examined in The Maastricht study [30]. This study showed the existence of microvascular dysfunction in both diabetes and prediabetes patients when compared to a group with normal glucose metabolism.

The treatment of the patients could be an explanation for our results. Specifically, the microvascular changes induced by T2D could be altered by an optimal medication [6, 31], which is supported by a study by Lynch FM et al. [32]. In the Lynch study, a group of CABG treated patients were examined by analyzing coronary resistance vessels (50–150 μM in diameter) in vitro with myography. No differences were found in lumen diameter, wall thickness, or wall-to-lumen ratio in patients with T2D (with or without hypertension) compared to a group without T2D. Lynch FM et al. stated that the medical treatment was the reason for this result.

Our T2D population was treated with statin, antihypertensive drugs, and antiglycemic drugs. These drugs could have influenced microcirculation. It should be noted that the medical treatment in the two groups was not significantly different (data not shown).

5. Limitations

This study is limited to a single medical center and is a substudy. The two groups compared are similar in respect to all other parameters other than the explored factors. The population studied was asymptomatic and likely had a lesser degree of CMD.

The assumption that T2D patients with albuminuria have a degree of CMD is a limitation of this study, although the concept has been proven by other studies. For T2D patients, the CMD is dependent on the presence of other risk factors, microvascular target organ damage, and T2D duration. The T2D patients enrolled in our study were heterogeneous regarding the risk factors’ distribution and end organ complications, which was also reflected in the heterogeneity of microangiopathy.

FFRct was possibly unaffected by the microvascular function, which means that our result is not due to the lack of CMD. FFRct could be affected by small differences in plaque morphology and degree of stenosis, even though no patient in the study had significant stenosis and the mean CAC score was equal between groups. While CMD can influence FFRct, it is the discrete stenosis in the coronaries that carry the burden of lowering FFRct and not the CMD. As such, the premise of using FFRct as a surrogate measurement of CMD is questionable; however, a study with a larger, more homogeneous population and with direct measure of CMD is needed.

6. Conclusions

In this observational study, we did not find FFRct to be affected by CMD. If this result is a consequence of no difference in CMD among patients, the unsuitability of FFRct for the assessment of CMD is to be explored in future studies.

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(Johanna Larsson) and K.E.; formal analysis, J.L. (Jess Lambrechtsen), L.J.H. and G.P.; investigation, L.J.H., G.P. and J.L. (Johanna Larsson); writing—original draft preparation, J.L. (Jess Lambrechtsen); writing—review and editing, J.L. (Jess Lambrechtsen); visualization, J.L. (Jess Lambrechtsen); supervision, K.E.; project administration, K.E. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Regional Ethics Committee for Southern Denmark (ID S-20150029).

Informed Consent Statement: Permission for the present study was given by the Regional Ethics Committee for Southern Denmark (ID S-20150029) and written consent was available for all participants.

Data Availability Statement: All data for the study group is available and is stored in a database located in Open Patient data Explorative Network (OPEN), Klinisk Institut Syddansk Universitet (Clinical Institute of Southern Denmark University Denmark). The data are available on reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

- T2D type 2 diabetes mellitus
- CMD coronary microvascular dysfunction
- FFRct fractional flow reserve assessed by coronary computed tomography angiography
- CCTA coronary computed tomography angiography
- ACR albumin–creatinine-ratio
- HR heart rate
- CAC coronary artery calcium

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