Noninvasive Skin Intrinsic Fluorescence Correlates With Degree of Coronary Artery Calcification

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Introduction

Noninvasive skin intrinsic fluorescence (SIF) measurements have previously been shown to correlate with coronary artery calcification (CAC) in subjects with type 1 diabetes.[1] Subjects with diabetes are assumed to be at higher risk for coronary artery disease (CAD) and more likely to have significant levels of CAC relative to subjects without diabetes. We undertook a study of subjects without previously diagnosed diabetes or cardiovascular disease to see if SIF was associated with CAC in this group.

Background

- Objective measures of myocardial infarction (MI) risk in asymptomatic patients are highly desired because approximately half of those that suffer an initial MI will die from the MI
- CAC is a strong, objective and independent risk indicator for MI
- There is resistance to large scale screening for MI risk using CAC because of access, cost and ionizing radiation exposure
- Noninvasive SIF measurements of dermal advanced glycation endproducts (AGEs) and oxidative stress markers have been associated with CAC and CAC progression in type 1 diabetes[1]
- SIF measurements contain multiple potential sources of information on the development of CAC
  - ❖ Spectral signatures from fluorophores in the epidermis and dermis (*eg* fluorescent AGEs, NADH, flavoproteins, lipo pigments, collagen and elastin crosslinks)
- SIF measurements are:
  - ❖ Non-ionizing
  - ❖ Much less expensive than CAC
  - ❖ Provide point-of-care results in under a minute
- SIF may be a potential screening tool for identification of clinically significant CAC in asymptomatic patients with intermediate Framingham risk scores
  - ❖ Positives would be sent for confirmatory a CAC scan to potentially reclassify the patient as low or high risk for MI

Study Aim

- Assess the ability of skin intrinsic fluorescence to detect clinically significant levels of coronary artery calcification in at-risk subjects without previously diagnosed diabetes or cardiovascular disease

Inclusion Criteria

- Men: Age ≥ 45 yrs referred to the New Mexico Heart Institute (NMHI) for measurement of CAC

Or

- Women: Age ≥ 50 yrs referred to NMHI for CAC measurement

And

- No pre-existing diagnosis of type 1 or type 2 diabetes or cardiovascular disease

All subjects gave informed consent and were recruited opportunistically from the New Mexico Heart Institute clinical practice when they reported for measurement of CAC.

The vast majority of subjects were at intermediate Framingham risk for coronary artery disease.

Characteristics of Study Participants

- The cohort consisted of 92 males (59.7±7.5 yrs) and 99 females (61.1±7.2 yrs) of which 156 were white, 32 Latino and 3 other
- Table 1 shows CAC as a function of certain cohort characteristics

	N (%)	Positives CAC	Negatives CAC	P Value
Female Gender	99 (52%)	108.7 ± 247.6	367.0 ± 893.0	0.0062
Never Smoked	100 (53%)	197.9 ± 424.9	260.5 ± 843.5	0.52
Dyslipidemia	98 (52%)	248.4 ± 793.6	210.8 ± 470.0	0.70
Hypertension	63 (33%)	205.9 ± 358.7	240.6 ± 764.0	0.73
Cancer	24 (13%)	265.2 ± 227.3	224.9 ± 697.4	0.78
Current Smoker	8 (4%)	274.6 ± 140.5	225.3 ± 670.7	0.84

Table 1: CAC values (mean ± SD) for characteristics of study participants

Measurement Methods

- The SCOUT DS device (Figure 1) measures light in the range of 360 to 660 nm and excites skin fluorescence with light emitting diodes (LED) centered at 375, 405, 417, 435 and 456 nm
- The SCOUT DS device also measures skin reflectivity with a white LED and uses these data to compensate for absorption due to subject-specific melanin and hemoglobin content
- Skin fluorescence and reflectance are measured noninvasively on the left volar forearm (Figure 1)
- CAC (standard Agatston score) was measured on a Toshiba Aquilion 64 slice CT scanner

Figure 1: SCOUT DS device
CAUTION – Investigational device. Limited by United States law to investigational use.

Analysis

- Used SIF from 456 nm excitation, 495 to 655 nm emission
- The emitted fluorescence was intrinsically corrected according to the method of Hull[2] with K_x=0.7, K_m=0.9, summed and then multiplied by 1000 to produce SIF
- CAC was square root transformed (SQRT) before computation of Pearson correlation coefficients[3]
- Receiver operating characteristics (ROC) curves were calculated for SIF and chronological age by sweeping the test threshold from maximum to minimum values and computing the corresponding sensitivities and specificities
- The area under the ROC curve (AUC) was computed by the Mann-Whitney statistic

Results

- CAC scores ranged from 0 to 6060, with a mean of 233
- Table 2 contains the mean ± SD of SIF, age, BMI and waist circumference for subjects with CAC < 300 and CAC ≥ 300 and correlation with the SQRT of CAC
  - ❖ SIF and age were significantly correlated with SQRT of CAC
- Figure 2 shows the ROC for SIF detection of CAC scores ≥ 300 (subject age included for reference)

	CAC < 300	CAC ≥ 300	Correlation w/ SQRT (CAC)	P Value
N	156	35	n/a	n/a
SIF (AU)	0.8 ± 0.1	1.0 ± 0.2	0.48	4.9E-15
Age (yrs)	59.5 ± 7.4	64.6 ± 7.7	0.27	0.00031
BMI (kg/m²)	27.3 ± 4.9	26.6 ± 5.1	-0.07	0.48
Waist (in)	35.0 ± 9.6	34.8 ± 12.4	-0.01	0.93

Table 2: Correlation and association of continuous variables with CAC

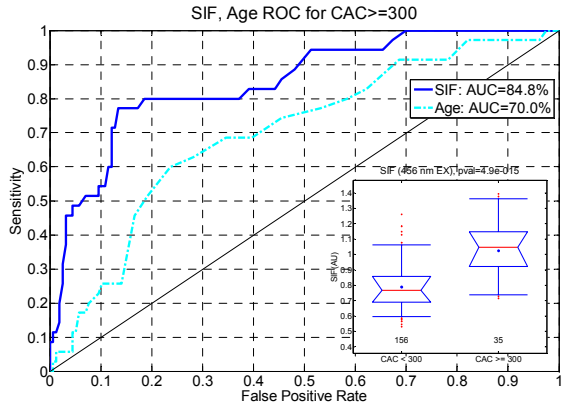

Figure 2: SIF and Subject Age ROCs for detection of CAC ≥ 300

Summary

- The SIF AUC of 84.8% is significantly better than that produced by using subject age (70.0%)
- SIF was 80% sensitive and 80% specific for detection of CAC ≥ 300

Conclusion

Noninvasive skin intrinsic fluorescence is correlated with clinically significant levels of CAC in at-risk subjects without a pre-existing diagnosis of diabetes or cardiovascular disease. Additional studies are warranted to further develop and understand the clinical utility of the SIF measurement for coronary artery disease risk assessment.

References

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