4. Beyond 64-slice MDCT
4-1. Dual Source CT

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Dual Source CT

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Summary

Temporal resolution is the most important factor in cardiac CT. Dual source CT dramatically improves conventional temporal resolution because there are two sets of X-ray tubes and detectors in a single CT device. Furthermore, the dual energy imaging obtains information on coronary blood flow as well as the morphology of coronary arteries. We describe the clinical applications of SOMATOM Definition Flash in this section.

拍動し続ける心臓をターゲットとする心臓CTにおいて、時間分解能が最も重要なファクターであることはいうまでもない。Dual source CTは、1台のCT装置の中に2組のX線収集系、つまりX線管球および検出器を搭載することで、従来の時間分解能を飛躍的に向上させた。また2管球それぞれから異なるエネルギーのX線を照射することによって得られるdual energyイメージングは、冠動脈の形態的評価だけでなく、ヨード造影剤を指標とした血流分布という付加情報をもたらす。この項では検出器列が0.6mm×128列となり、ガントリー回転速度が0.28秒に高速化されたSOMATOM Definition Flashを中心に、その臨床応用について述べる。

撮影法

SOMATOM Definition Flashにおける心臓CTの撮影方法には、従来からのConventional Spiral、step and shoot撮影と機能診断のための低被曝撮影を組み合わせたFlash Cardio Sequence、これに加え2管球それぞれが描くらせん軌道を組み合わせることで、これまでにない高いヘリカルピッチでの撮影を可能にしたFlash Spiral Cardioの3種類が用意されている。心拍数や不整脈の有無、検査目的などに応じて、これらの中から適切な撮影法を選択して検査を行うことになる。

1. Conventional Spiral

X-flying focal spot機構に対応した検出器は0.6mm×128列のものとなり、ガントリー回転速度も0.33秒から0.28秒に高速化された。Dual Source CTの特徴はその高い時間分解能にあり、ハーフ再構成に2組のX線収集系を生かすことにより、常時75msecの時間分解能が得られている。したがってこれまでのようなβ-ブロッカーを用いた心拍コントロールは必要なく、検査前処置に時間をとられたり、緊急検査に対応できなかったりすることはない。また心房細動を含めた不整脈症例に対しても有効である。高心拍数の状態で撮影を行うことは被曝低

減にもつながっている。サンプリングデータの冗長性を保つために、低心拍例においてはヘリカルピッチを高く設定できないが、高心拍例においてはこれを高めても体軸方向でのデータ欠損を生じないため、心拍数の増加に応じてヘリカルピッチを上げることができる。これは撮影時間の短縮つまりは被曝低減を意味する。

2. Flash Cardio Sequence

Step and shoot撮影であるこのモードにおいては、3〜4心拍の撮像で心臓全体をカバーすることになる。不整脈に対しては、これを避けるように撮影を遅延させることで対応が可能であるが、70bpm程度までの比較的安定した心拍が得られている場合に選択される。被曝線量は120kvを用いた撮影で2.6msV、同等の造影効果が得られる条件下の100kvを用いた撮影では1.2mSvという低線量での撮影が可能である[1]。

3. Flash Spiral Cardio

心電図同期画像再構成法を用いる心臓CTでは、得られた画像データの中から再構成に必要な一部の心時相におけるデータを選択して用いている。したがってデータの冗長性を保つためには、通常の非心電図同期撮影と比較し、ヘリカルピッチを低く設定し、データ密度の低下を避けなければならず、これが心臓CTにおける被曝量の増加につながっている。

Dual source CTは同一装置の中にX線管球と検出器というX線収集系を2組もつが、これらが描くらせん軌道が互いを補い合うような軌道を通過すれば、ヘリカルピッチをたとえ大きくしても体軸方向におけるサンプリングデータの欠損を防ぐことができる(図1)。これを応用した撮影方法がFlash Spiralである。ヘリカルピッチを3.2にすることで、2組のX線収集系のらせん軌道が相補して、中心部のFOVに関してはデータ欠損を防ぎ、再構成画像を得ることができる。43cm/secの高速で撮影範囲をカバーすることになり、胸部撮影における呼吸運動、小児における体動などの影響を最小限に抑えることが可能となっている。

この撮影モードでは心臓CTにおける標準的撮影範囲約10cmをカバーするのに必要な撮影時間は0.25秒であり、この撮影時間に相当する静止時間が得られるような状態の心拍であれば、心臓CTにも応用することが可能となる。心臓撮影用に用意されたFlash Spiral Cardioは心電図同期下に拡張期の心拍静止時相に合わせてこのFlash Spiralを行うモードである。0.25秒程度の静止時相が必要であり、適応は60bpm程度までの安定した心拍であることが条件となるが、1心拍内の静止時相のみで冠動脈全体のCTA撮影を終えるため、冠動脈CTAで問題となるblurringやbanding artifactから開放された再構成画像が得られる(図2)。X線照射時間が0.25秒であることから、被曝も著明に低減され、1mSv前後での撮影が可能となっており、被曝量の比較対象はこれまでの冠動脈造影ではなく非心電図同期の胸部CT検査となろう。被曝の低減が得られるからといって安易に多時相の撮影を行うことには問題があるが、CTO症例における側副血行路描出能の向上(図3)や、perfusion評価などへの応用が期待される。

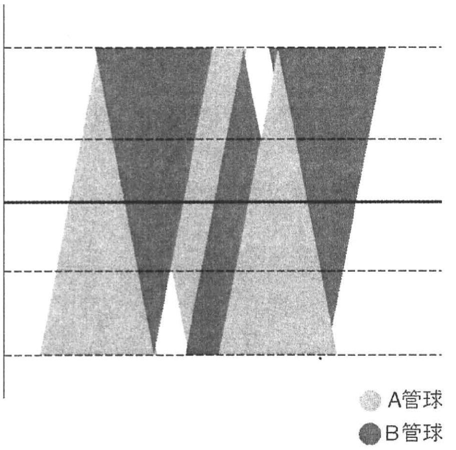

図1　Flash Spiral
2組のX線収集系が別々のらせん軌道を描くことにより，FOV中心部においては体軸方向でのデータ欠損を生じない．

造影法

造影剤は冠動脈末梢の描出能を高めるために、従来と同様に370mgI/mLの高濃度造影剤を用いている。注入速度は体重に従い0.07mL/kg/secを採用しており、造影剤の到達時間、撮影時間に従い、総投与量を決定している。これが基本となるが撮影時の心拍数や造影剤注入ルートの状態などにより、注入速度や総投与量を増減している。特にBMIが低く、造影剤注入ルートの状態により注入速度を上げられない場合などに、80kVあるいは100kVによる撮影を行っており、これにより診断に足

図2　70歳代　男性，OMI
A　冠動脈CTA angiographic view：Banding artifactは認められず，RCAのCTO病変が明瞭に描出される．
B　冠動脈CTA 横断像：RCAにはblurringを伴わず，CTO病変が明瞭に描出されている．

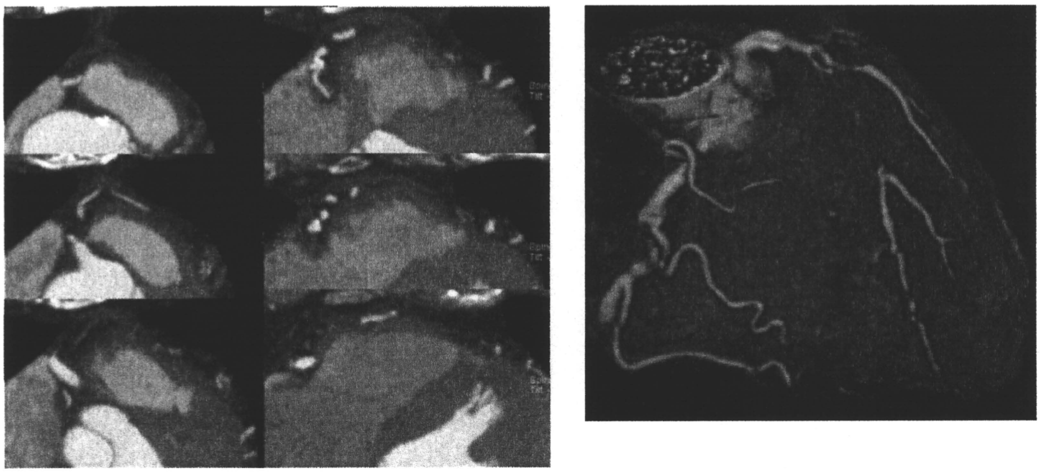

図3　60歳代　男性，OMI
A　冠動脈CTA 横断像，B　VR像：LAD#6～7のCTO病変が認められ，RCA conus branchよりLAD末梢への側副血行路が描出されている．多時相撮影を行うことにより，側副血行路描出能の改善が期待できる．

る冠動脈内腔のコントラストを保っている(図4)。

SOMATOM Definition Flashにおいては、呼吸停止直後の心拍変動期を避けるために、呼吸停止後5秒間のdelay timeが設けられており、この間の造影剤の動態を知ることができない。また上記のFlash Spiral Cardioでは撮影時間はわずか0.25秒であり、適切な造影タイミングをあらかじめ知ることは以前にも増して重要となっている。したがって現在はtest injection法を使用し、撮影開始時間や造影剤注入時間を設定している。

正診度

Dual Source CTを用いた冠動脈CTAの正診率に関しては、すでに多くの報告がみられ、感度88～95%、特異度92～99%、陽性的中率68～81%、陰性的中率97～99%と述べられている[2-6]。これまでのβ-ブロッカーを併用した64列MDCTによる報告(感度82～99%、特異度90～98%、陽性的中率56～97%、陰性的中率92～100%)[7-15]と同等の結果が得られており、2管球による時間分解能の向上がこれに寄与している。当院における

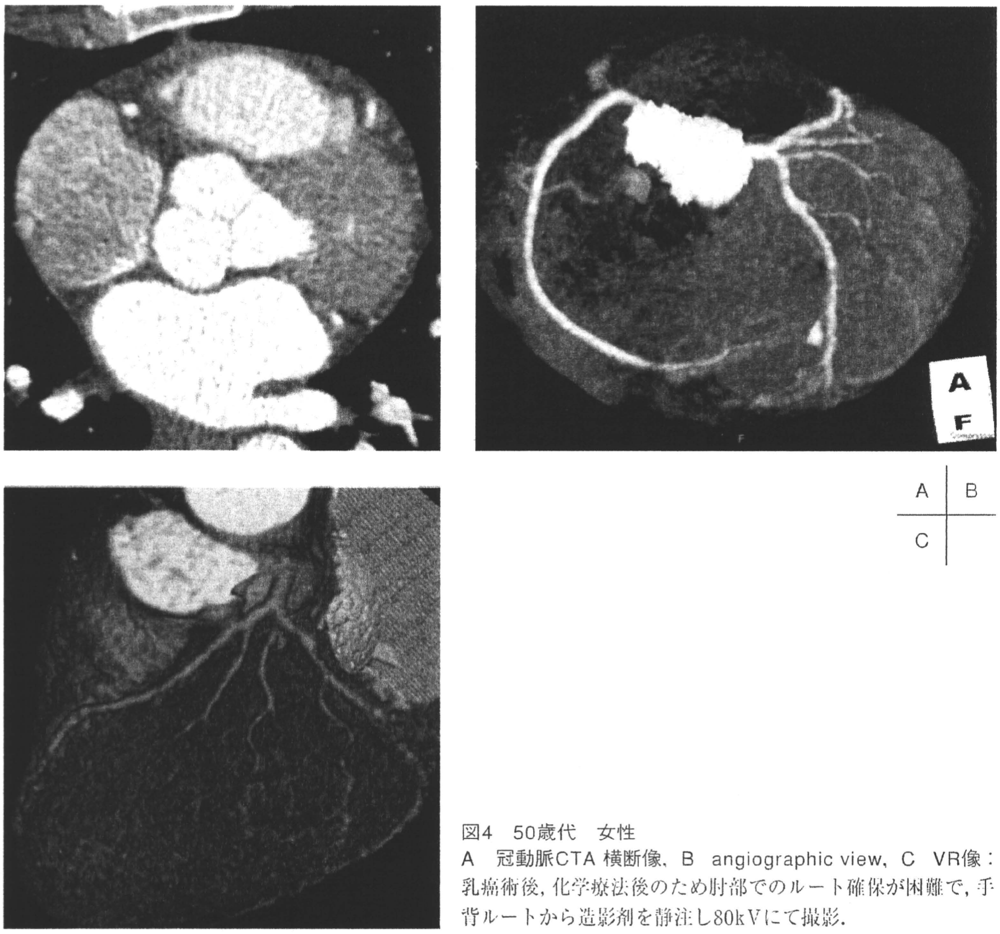

図4　50歳代　女性
A　冠動脈CTA 横断像、B　angiographic view、C　VR像：乳癌術後，化学療法後のため肘部でのルート確保が困難で，手背ルートから造影剤を静注し80kVにて撮影．

冠動脈造影との比較検討においても、70bpm以上の高心拍数群で、感度91%、特異度99%、陽性的中率95%、陰性的中率99%を示しており[16]、高心拍症例に対するDual Source CTの有用性は高い(図5)。

不整脈例への対応

時間分解能に優れるDual Source CTは、高心拍例においてもマルチセクタ再構成を必要としないため、不整脈例における有用性も高い。Oncelらの心房細動症例に対する初期検討においても、感度80～87%、特異度98～99%、陽性的中率77～80%、陰性的中率99%と報告されており、高い陰性適中率は維持されている[17]。再構成画像は1心拍内に得られた画像データからのみ作成されるため、再構成心時相のずれからbanding artifactを生じる場合はあっても、複数心拍の画像データから再構成を行った際に認められるようなblurringを生じることは少ない。しかし頻脈性不整脈例においては、画像再構成に最適な静止心時相を得ることができない心拍が含まれてくる場合があり、データの冗長性を担保するためにヘリカルピッチを低く設定せざるを得ず、被曝の増加は避けられない。

Dual-energyの可能性

異なるエネルギーのX線を用いることによって物質の減弱係数は変化するが、物質の組成によってその程度が異なる。このことを利用して造影剤、骨、靱帯などの

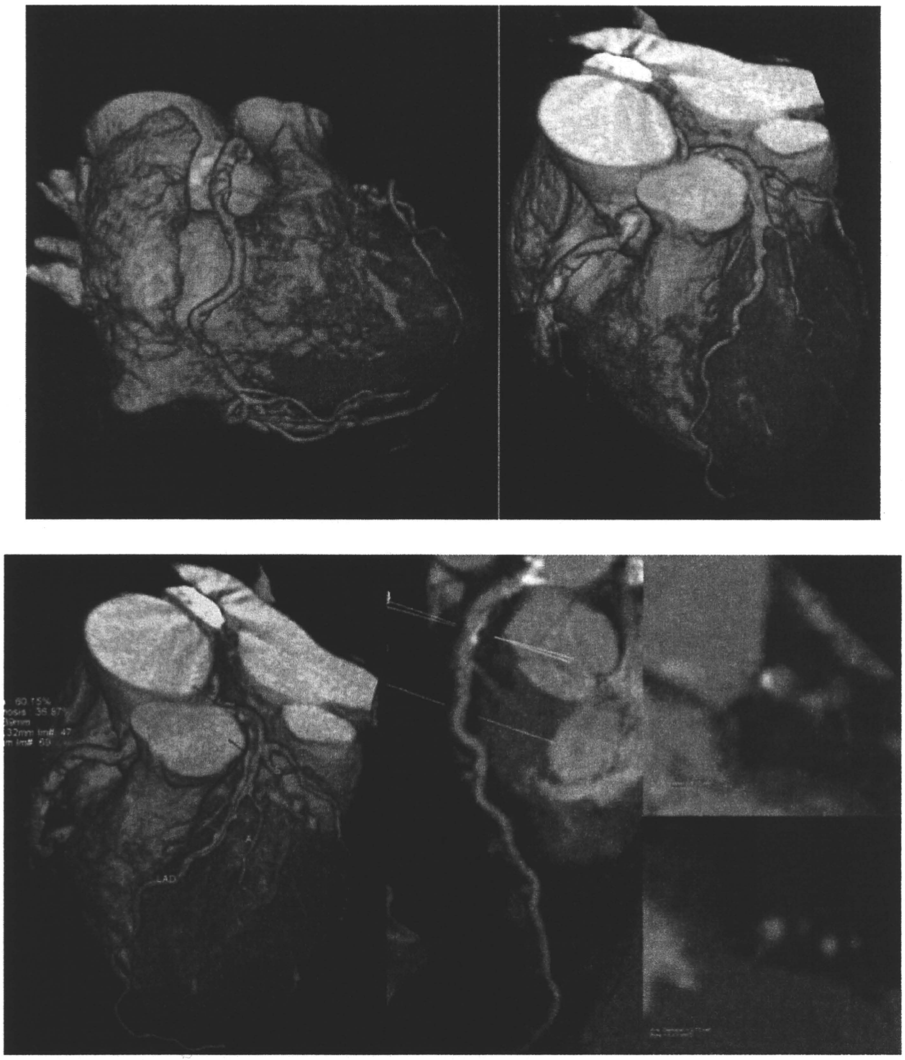

図5　60歳代　女性
A　冠動脈CTA VR像，B　VR像，LADのCPR像，短軸横断像：平均心拍数120の高心拍例であるが，banding artifactは認められない．

A
B

特定の物質、組織を分離表示させる手法がdual energyイメージングである。しかし実際に管球から照射されるX線は単一組成ではなくスペクトルとして存在しており、80kv、140kv両者の帯域には重なり合う部分が多く、分離能の低下や被曝の増加をきたしていた。そこでSOMATOM Definition Flashにおいては、140kvにおける低電圧スペクトルをカットするselective photon shieldと呼ばれる物理フィルターが導入され、画質の向上が図られている。この効果は高画質化に貢献するばかりでなく、同時に被曝量の低減にも寄与しており、通常の撮影と同等の被曝量でdual energyイメージングが可能となり、より臨床応用に活用しやすい環境が整えられた(図6)。

CTAでは、造影後CT像から非造影CT像を得るvirtual non-contrast法や、血管周囲の骨構造や血管壁の石灰化病変の除去などに応用されている。心臓CT領域においては、冠動脈CTAで検査開始初期段階から継続して問題となっている高度石灰化病変の評価において、その石灰化除去による診断能の向上が期待されている。また左室心筋に分布する造影剤を分離可視化できることか

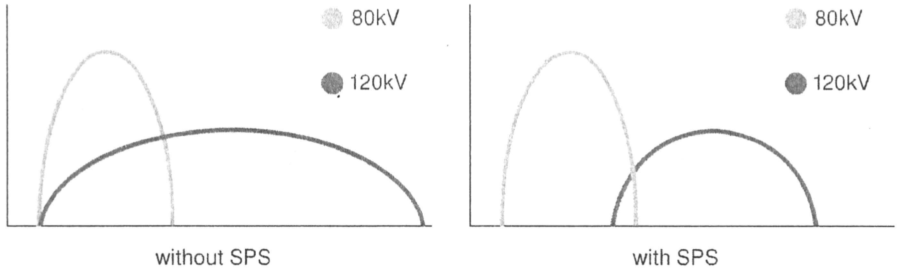

図6　Selective photon shield (SPS)
140kVのX線束に対しselective photon shieldを用いることにより，二つのX線エネルギーのスペクトルの重なりが減少し，画質の向上と被曝低減が得られる．

ら、心筋血流分布の評価が期待されている。しかし実際にdual energyイメージングとして用いる場合には、2管球を異なるエネルギーの管球として別々に用いなければならないことが問題となる。非心電図同期撮影においては、1管球の360°データを用いて画像再構成を行っており、dual energyイメージングとして撮影しても時間分解能の変化はない。一方、心電図同期下の心臓CTにおいては、時間分解能を高めるために、2管球それぞれで得られる90°データを合わせることで、ハーフ再構成に必要な180°データを得ている。冠動脈CTAとしての形態評価においては、異なるコントラストや信号・ノイズ比をもつ80kvおよび140kvの90°データに対し、両者を近づけるような再構成処理を行い、データを合わせることで、75msecの時間分解能が保たれている。しかしdual energyイメージングとしての演算処理を必要とする画像においては、時間分解能の低下は避けられない。このことは造影剤の心筋血流分布を評価することにおいて問題とはならないかもしれないが、冠動脈CTAにおける石灰化病変の除去に関しては依然検討の余地がある。

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ORIGINAL ARTICLE

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Enjoying hobbies is related to desirable cardiovascular effects

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Abstract An unhealthy lifestyle can increase the risk of cardiovascular disease. However, the mechanism by which lifestyle influences the development of cardiovascular disease remains unclear. Since coronary endothelial function is a predictor of cardiovascular prognosis, the goal of this study was to characterize the effect of enjoying hobbies on coronary endothelial function and cardiovascular outcomes. A total of 121 consecutive patients (76 men, 45 women) with almost normal coronary arteries underwent Doppler flow study of the left anterior descending coronary artery following sequential administration of papaverine, acetylcholine, and nitroglycerin. On the basis of responses to questionnaires, patients were divided into two groups; the Hobby group ($n = 71$) who enjoyed hobbies, and the Non-hobby group ($n = 50$) who had no hobbies. Cardiovascular outcomes were assessed at long-term follow-up using medical records or questionnaire surveys for major adverse cardiovascular events (MACE).The average follow-up period was 916 ± 515 days. There were no significant differences in demographics when comparing the two groups. The percent change in coronary blood flow and coronary artery diameter induced by acetylcholine was significantly greater in the Hobby group than in the Non-hobby group (49% ± 77% vs 25% ± 37%, $P < 0.05$, 4% ± 13% vs −3% ± 20%, $P < 0.05$, respectively). The MACE rate was significantly lower in the Hobby group than in the Non-hobby group ($P < 0.01$). Enjoyment of hobbies was the only independent predictor of MACE (odds ratio 8.1 [95% confidence interval 1.60, 41.90], $P = 0.01$) among the variables tested. In the early stages of arteriosclerosis, enjoying hobbies may improve cardiovascular outcomes via its favorable effects on coronary endothelial function.

Key words Hobby · Coronary · Endothelial function · Cardiovascular · Major adverse cardiovascular event

Introduction

Endothelial dysfunction is present in the coronary and peripheral arteries in patients with chronic heart failure (CHF).[1,2] An important consequence of endothelial dysfunction is an impairment in nitric oxide (NO) release,[3] which results in the inability of a vessel to dilate in response to various physiological stimuli. Accumulating evidence suggests that endothelial dysfunction contributes to exercise intolerance, impaired myocardial perfusion, and left ventricular remodeling in patients with CHF. In patients with previous myocardial infarction, exercise training improves endothelium-dependent vasodilation, and this improvement is associated with a significant increase in exercise tolerance.[4] Further, NO has antiarteriosclerotic properties, and endothelial dysfunction is an independent risk factor for cardiovascular disease, including hypertension, peripheral vascular disease, and coronary artery disease.[5,6]

Endothelial function may also vary with lifestyle, including physical activity, stress, and quality of life. Indeed, interventions with an aggressive focus on lifestyle changes (smoking cessation, diet, exercise, and avoiding stress) produce favorable cardiovascular outcomes in patients treated with percutaneous coronary intervention.[7] Further, modifiable lifestyle factors (smoking, physical activity, and body mass index) in middle-aged men play an important role in long-term survival free of cardiovascular disease and diabetes.[8] Life stress is also thought to alter the dynamic regulation of the autonomic, neuroendocrine, and immune

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A portion of this study was presented at the 56th American College of Cardiology Meeting, 2007.

systems, and high stress contributes to a higher risk of mortality from ischemic heart disease in younger men.[9]

Enjoying hobbies may relieve stress and increase quality of life. For example, Sivasankaran et al. reported that yoga and meditation programs improve endothelial function in patients with coronary artery disease.[10] However, the relationship among enjoying hobbies, coronary endothelial function, and cardiovascular prognosis remains unclear. Therefore, the goal of this study was to characterize the effect of enjoying hobbies on coronary endothelial function and cardiovascular outcomes.

Subjects and methods

Patients

One hundred and twenty-one patients (mean age ± SD 62.0 ± 12.8 years, age range 17–80 years; 76 men, 45 women) with angiographically normal or near-normal (% diameter stenosis <30%) epicardial coronary arteries characterized in the course of cardiac catheterization for investigation of chest pain or abnormal noninvasive examinations were enrolled in this study.

Procedures

Pharmacologic-induced vasodilating function was assessed with a Doppler guide wire and represented as a change in coronary blood flow and coronary artery diameter. Study inclusion criteria were: (1) presence of angiographically smooth arteries, (2) mild irregularities with no coronary artery lesion >30% lumen diameter stenosis by visual assessment in major epicardial vessels, (3) proximal coronary arteries >2.0 mm, and (4) presence of single, discrete, and circular lesion with a smooth reference lesion.[11] Patients with previous myocardial infarction, previous coronary revascularization, or variant angina were excluded. Cardiac medications were withheld for at least 48 h before the study. Written informed consent was obtained from all patients before catheterization in accordance with guidelines established by the Committee for the Protection of Human Subjects at our institution. Diagnostic coronary angiography was performed using a 6-F Judkins catheter with a standard femoral artery percutaneous approach. Five thousand units of heparin were administered at the beginning of the procedure. Nonionic contrast material was used for all patients. No nitroglycerin was given prior to diagnostic procedures. Coronary blood flow (CBF) response to papaverine, acetylcholine (ACh), and nitroglycerin was studied according to protocols described previously.[12–14] After completion of the diagnostic catheterization, interventions were performed as follows: (1) introduction of a 0.014-inch Doppler guide wire (Cardiometrics, Santa Ana, CA, USA) into the left anterior descending coronary artery; (2) after obtaining a stable Doppler signal, a bolus of papaverine (an endothelium-independent vasodilator in resistance coronary arteries; 12.5 mg/5 ml) was injected through a catheter; and (3) infusion of ACh (an endothelium-dependent vasodilator in resistance and epicardial coronary arteries; 0.5 ml/min) at dosages of either 3 or 30 μg/min for 2 min via the catheter.[14,15] Drugs were infused at least 5 min apart. Coronary arteriography was performed before and immediately after infusion of each agent. Phasic coronary blood flow velocities, arterial blood pressure, and heart rate were monitored continuously and recorded. Measurements obtained during steady state conditions were used as control values for later analysis.

Assessment of pharmacologic-induced coronary vasodilating function

Doppler flow velocity spectra were analyzed on-line to determine time-averaged peak velocity. Volumetric CBF was determined from the formula: CBF = cross-sectional area × average peak velocity × 0.5.[16] Coronary flow reserve to papaverine was calculated as the ratio of maximal CBF induced by papaverine to basal CBF, which was equivalent to the endothelium-independent function of the resistance coronary artery. Change in coronary artery diameter (CAD) in response to nitroglycerin, which reflects the endothelium-independent function of the epicardial coronary artery, was also calculated by similar methods. Endothelium-dependent function of the resistance coronary artery was calculated as the percent increase in CBF in response to ACh, and the percent increase in CAD induced by ACh was calculated as estimation of endothelium-dependent function of the epicardial coronary artery.[12–14]

Long-term follow-up

Data for clinical long-term follow-up were obtained from hospital charts and through telephone interviews with patients, conducted by trained reviewers who were blinded to treatment assignment. Informed consent was obtained from all patients to allow use of these data for study analyses. Compliance was assessed and confirmed via patient interview by the physician upon hospital admission.

Study patients were assigned to either the "Hobby group" or "Non-hobby group" based on the response to the question, "Have you engaged in any pleasurable hobbies for more than one year?" The Hobby group was further subdivided into the Outdoor-hobby group and Indoor-hobby group. The following clinical events were reported as major adverse cardiovascular events (MACE): cardiac death, hospitalization due to heart failure, occurrence of fatal arrhythmia or myocardial infarction, or need for percutaneous coronary intervention or coronary artery bypass grafting. The first MACE was used for analysis. If a primary end point was reached, information regarding potential cardiovascular events was validated by review of source data. The decision that a patient had reached a primary end point was made only after reviewing the medical records. The relationship between questionnaire results, coronary endothelial function, and cardiovascular prognosis were fully examined.

Coronary endothelial function and cardiovascular prognosis

Patients were divided into one of two groups according to ACh responsivity of epicardial and resistance coronary arteries. At the level of epicardial coronary artery, patients were subdivided into one of two groups: the Normal ACh CAD response group (n = 65), reflecting an increased percent increase in CAD in response to ACh, and the Poor ACh CAD response group (n = 56), reflecting a decreased percent increase in CAD in response to ACh. Further, at the resistance coronary vessel level, patients were subdivided into one of two groups: the Normal ACh CBF group, reflecting a percent increase in CBF >50% (n = 37), and the Poor ACh CBF response group, reflecting a percent increase in CBF <50% (n = 84). Cardiovascular outcomes were compared between the two groups.

Statistical analysis

All measurements and analysis were performed in a blinded fashion. Statistical analysis was performed with StatView, version 5.0 (SAS Institute, Cary, NC, USA). Comparisons between variables and between groups were conducted by Student's regression analysis unpaired/paired t-test or the two-tailed multiple t-test with Bonferroni correction following analysis of variance. Event-free survival curve was analyzed with Kaplan–Meier methods, and the P value was obtained using Cox regression analysis. Multivariate regression analysis was performed to identify the effects of enjoying hobbies and the classical risk factors for MACE as independent predictors of cardiovascular prognosis. A two-tailed probability value of less than 0.05 was considered statistically significant. Results are expressed as mean ± SD unless otherwise indicated.

Results

A total of 121 patients were enrolled in this study (76 male, 45 female,). The mean age was 62.0 ± 12.8 years (range, 17–80 years). Questionnaire responders who enjoyed hobbies had a significantly greater MACE-free ratio and improved coronary endothelial function when compared with those that did not enjoy hobbies (97.2% vs 82.0%, $P < 0.05$). The Hobby group consisted of 71 patients who enjoyed hobbies, and the Non-hobby group consisted of 50 patients who did not have hobbies. Hobby details are summarized in Table 1. One hundred and twenty-one patients enjoyed a total of 157 hobbies; 81 of which were indoor hobbies and 76 of which outdoor hobbies (1.3 hobbies per patient). Twenty-one patients enjoyed only outdoor hobbies, 32 patients enjoyed only indoor hobbies, and 18 patients enjoyed both types of hobbies. Thirty-one patients, including 18 patients who enjoyed both types of hobbies, enjoyed outdoor hobbies (Outdoor-hobby group). Fifty patients, including 18 patients who enjoyed both types of hobbies, enjoyed indoor hobbies (Indoor-hobby group). The other 50 patients had no hobbies.

Patient characteristics of both groups are summarized in Table 2. There was no significant difference in age, sex, body mass index, classical coronary risk factors, and systemic blood pressure when comparing the two groups. There were no significant differences in the proportion of patients who were taking angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, statins, calcium channel blockers, and aspirin when comparing the two groups.

Clinical characteristics of the two groups are summarized in Table 3. There was no significant difference in the total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting plasma glucose, hemoglobin A1c, and creatinine when comparing the two groups.

Table 4 shows the hemodynamic parameters of the two groups. There was no significant difference in left ventricular end-diastolic dimension, left atrial dimension, left ventricular ejection fraction, left ventricular mass, biventricular Tei index, heart rate, pulmonary capillary wedge pressure, mean pulmonary artery pressure, and cardiac index when comparing the two groups.

Changes in coronary blood flow

The percent increase in CBF induced by ACh was significantly greater in the Hobby group than in the Non-hobby

Table 1. Hobby details

Indoor hobby (n = 81)	Outdoor hobby (n = 76)
Reading books (n = 19)	Farming, gardening (n = 27)
Handicrafts, sewing (n = 8)	Fishing (n = 13)
Watching movies (n = 6)	Playing golf (n = 6)
Computer games (n = 6)	Going for a drive (n = 5)
Playing musical instruments (n = 5)	Jogging, walking (n = 4)
Playing the game of "Go" (n = 5)	Ground-golf (n = 3)
Taking care of a pet (n = 4)	Taking pictures or movies (n = 2)
Listening to music (n = 4)	Softball (n = 2)
Karaoke, chorus (n = 5)	Mini-volleyball (n = 2)
Cooking (n = 2)	Japanese croquet (n = 2)
Drawing pictures (n = 2)	Japanese dancing (n = 2)
Others (n = 15)	Others (n = 8)

Table 2. Comparison of patient characteristics between two groups

	Hobby group (n = 71)	Non-hobby group (n = 50)	P value
Age (years)	60.4 ± 11.9	64.3 ± 13.8	0.10
Sex, male/female	44/27	32/18	0.82
BMI	24.0 ± 3.4	23.0 ± 3.8	0.17
Systolic BP/diastolic BP	129 ± 21/75 ± 15	125 ± 23/72 ± 14	0.38
Coronary risk factors			
Smoking (%)	27 (38)	21 (42)	0.67
Hypertension (%)	41 (58)	33 (66)	0.60
Hyperlipidemia (%)	33 (46)	23 (46)	0.96
Diabetes (%)	13 (18)	9 (18)	0.97
Medical profile			
ACEI (%)	12 (17%)	13 (34%)	0.22
ARB (%)	15 (21%)	18 (36%)	0.07
Statin (%)	11 (18%)	3 (8%)	0.11
CCB (%)	28 (46%)	19 (49%)	0.87
Aspirin (%)	25 (41%)	12 (31%)	0.19

BSA, body surface area; BMI, body mass index; BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker

Table 3. Comparison of clinical characteristics between two groups

	Hobby group	Non-hobby group	P value
Laboratory data			
Total cholesterol (mg/dl)	195 ± 36	191 ± 32	0.57
Triglyceride (mg/dl)	116 ± 64	122 ± 68	0.62
HDL-cholesterol (mg/dl)	55 ± 16	57 ± 13	0.39
LDL-cholesterol (mg/dl)	119 ± 28	111 ± 30	0.16
Fasting plasma glucose (mg/dl)	105 ± 27	101 ± 16	0.47
HbA1c (mg/dl)	5.55 ± 1.07	5.56 ± 1.20	0.84
Creatinine (mg/dl)	0.80 ± 0.23	0.96 ± 0.86	0.15

HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c

Table 4. Comparison of hemodynamic parameters between two groups

	Hobby group	Non-hobby group	P value
Echocardiographic parameters			
LVDd (mm)	52.5 ± 9.4	52.9 ± 9.0	0.81
LAD (mm)	39.9 ± 8.0	41.8 ± 10.2	0.26
LVEF (%)	60.6 ± 15.8	61.0 ± 14.1	0.88
LV mass (g)	261.6 ± 107.6	264.4 ± 81.0	0.87
LV Tei index	0.55 ± 0.24	0.54 ± 0.25	0.81
RV Tei index	0.34 ± 0.15	0.39 ± 0.18	0.14
Hemodynamic parameter determined by Swan–Ganz catheter			
Heart rate (beats/min)	70.1 ± 10.5	68.7 ± 13.7	0.52
PCWP (mmHg)	8.8 ± 4.4	8.7 ± 4.9	0.91
MPAP (mmHg)	14.8 ± 4.0	15.4 ± 4.6	0.45
CI (l/min/m^2)	2.97 ± 0.56	2.78 ± 0.60	0.08

LVDd, left ventricular end-diastolic dimension; LAD, left atrium dimension; LVEF, left ventricular ejection fraction; LV, left ventricle; RV, right ventricle; Tei, total ejection isovolemic; PCWP, pulmonary capillary wedge pressure; MPAP, mean pulmonary artery pressure; CI, cardiac index

group (49% ± 77% vs 25% ± 37%, $P < 0.05$), but the baseline CBF did not differ when comparing the two groups (76 ± 40 ml/min vs 90 ± 56 ml/min, P not significant). The percent change in CBF induced by papaverine was comparable between the two groups (211% ± 109% vs 187% ± 112%, P not significant) (Table 5).

Changes in coronary artery diameter

The baseline coronary artery diameter was similar when comparing the two groups (2.9 ± 0.7 mm vs 3.0 ± 0.6 mm, P not significant). The percent change in CAD induced by ACh was significantly greater in the Hobby group than in

Table 5. Comparison of coronary hemodynamics between two groups

	Hobby group	Non-hobby group	*P* value
CBF at baseline (ml/min)	76 ± 40	90 ± 56	0.12
CAD at baseline (mm)	2.9 ± 0.7	3.0 ± 0.6	0.71
% change in CBF induced by papaverine (%)	211 ± 109	187 ± 112	0.24
% change in CBF induced by ACh (%)	49 ± 77	25 ± 37	0.04*
% change in CAD induced by ACh (%)	4 ± 13	−3 ± 20	0.02*
% change in CAD induced by NTG (%)	17 ± 17	11 ± 12	0.05

Values are mean ± SD
CBF, coronary blood flow; CAD, coronary artery diameter; ACh, acetylcholine; NTG, nitroglycerine
*Significant *P* value vs non-hobby group

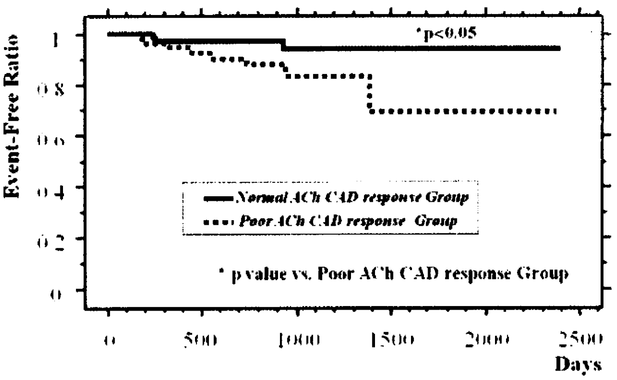


Fig. 1. Kaplan–Meier relationship between acetylcholine (*ACh*)-induced changes in coronary artery diameter (*CAD*) and outcomes; Normal ACh CAD response group versus Poor ACh CAD response group. *P* value was calculated with the log-rank test

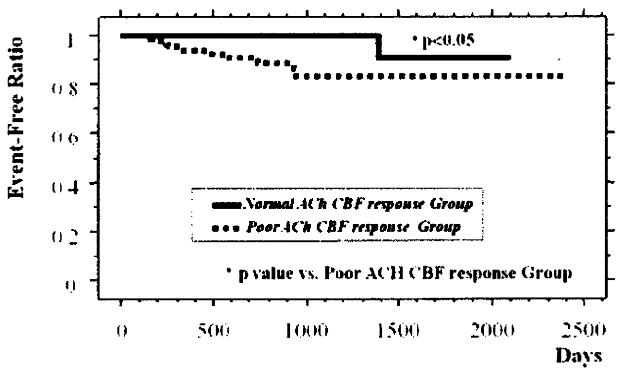


Fig. 2. Kaplan–Meier relationship between acetylcholine (*ACh*)-induced changes in coronary blood flow (*CBF*) and outcomes; Normal ACh CBF response group versus Poor ACh CBF response group. *P* value was calculated with the log-rank test

the Non-hobby group (4% ± 13% vs −3% ± 20%, $P < 0.05$). The percent change in CAD induced by nitroglycerin was not significantly different when comparing the two groups (17% ± 17% vs 11% ± 12%, *P* not significant) (Table 5).

Cardiovascular outcomes and coronary endothelial function

Major adverse cardiovascular events occurred in 11 patients: hospitalization due to heart failure in 6 cases, fatal arrhythmia in 2 cases, acute myocardial infarction in 2 cases, and percutaneous coronary intervention in 1 case. At the epicardial coronary vessel level, MACE occurred in 3 cases (4.6%) in the Normal ACh CAD response group and in 8 cases (14.3%) in the Poor ACh CAD response group. The MACE-free ratio was significantly greater in the Normal ACh CAD response group than in the Poor ACh CAD response group ($P < 0.05$) (Fig. 1).

At the resistance coronary vessel level, MACE occurred in only one case (2.7%) in the Normal ACh CBF response group and in 10 cases (11.9%) in the Poor ACh CBF response group. The MACE-free ratio was significantly greater in the Normal ACh CBF response group than in the Poor ACh CBF response group ($P < 0.05$) (Fig. 2).

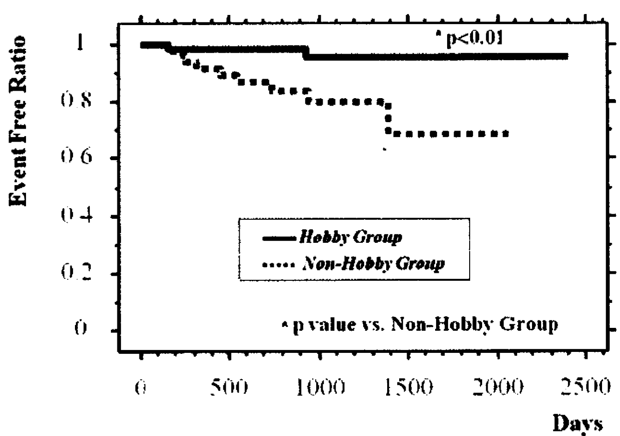


Fig. 3. Kaplan–Meier relationship between hobbies and outcomes; Hobby group versus Non-hobby group. *P* value was calculated with the log-rank test

Cardiovascular outcomes and hobbies

There were two incidences of MACE in the Hobby group and 9 in the Non-hobby group. The MACE-free ratio was significantly greater in the Hobby group than in the Non-hobby group ($P < 0.05$) (Fig. 3).

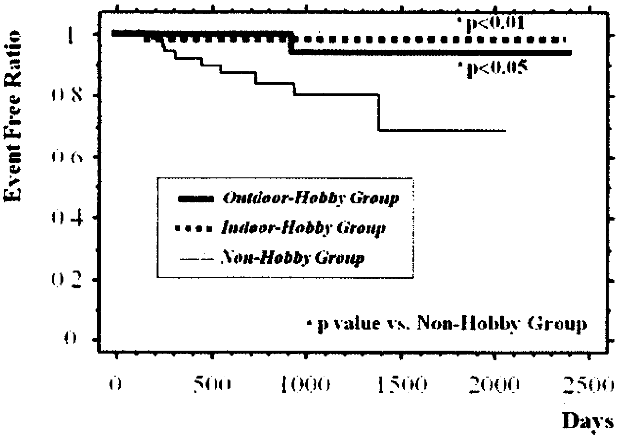


Fig. 4. Kaplan–Meier relationship between type of hobby and outcomes; Outdoor-hobby group versus Indoor-hobby group versus Non-hobby group. *P* value was calculated with the log-rank test

There was one incidence of MACE in the Outdoor-hobby group and one incidence of MACE in the Indoor-hobby group. The event-free ratio was significantly higher in the Outdoor-hobby group and Indoor-hobby group than in the Non-hobby group ($P < 0.05$ and $P < 0.01$, respectively) (Fig. 4).

Multivariate analysis and Cox proportional hazards ratio of MACE

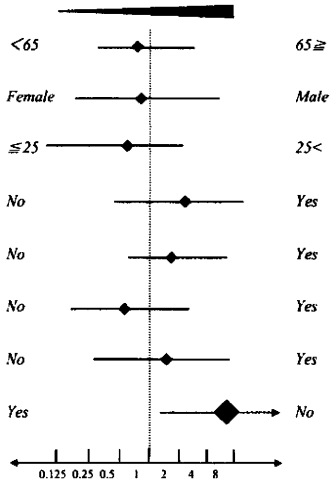
There were no significant differences in age, sex, body mass index, and major coronary risk factors when comparing the MACE group and Non-MACE group. However, the number of patients who enjoyed hobbies was significantly lower in the Non-MACE group than in the MACE group (18% vs 63%, $P < 0.01$) (Table 6). Of all the variables tested (age, sex, classical coronary risk factors, and hobbies), enjoying hobbies was the only independent predictor of MACE (odds ratio 6.74 [95% confidence interval 1.38, 32.91], $P = 0.02$) (Table 7).

Table 6. Parameters in association with MACE

Factor	MACE (+) $n = 11$	vs	MACE (−) $n = 110$	*P* value: Univariate regression analysis	*P* value: Multivariate regression analysis
Age	64.7 ± 19.4	vs	61.7 ± 12.0	0.46	0.99
Male	8 (73%)	vs	68 (62%)	0.48	0.91
Body mass index	21.8 ± 3.1	vs	23.8 ± 3.6	0.09	0.27
Current smoking	7 (64%)	vs	41 (37%)	0.09	0.22
Hypertension	8 (73%)	vs	66 (60%)	0.41	0.59
Hyperlipidemia	4 (36%)	vs	52 (47%)	0.49	0.80
Diabetes mellitus	2 (18%)	vs	20 (18%)	0.99	0.80
Hobby	2 (18%)	vs	69 (63%)	0.004*	0.01*

MACE, major adverse cardiovascular events
*Significant *P* value vs MACE (+)

Table 7. Hazard ratio of parameters to MACE



			Univariate			Multivariate		
			Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age	*<65*	*65≧*	1.62	(0.47–1.62)	0.44	0.79	(0.20–3.11)	0.79
Sex	*Female*	*Male*	1.63	(0.43–6.14)	0.47	0.90	(0.16–5.09)	0.91
BMI	*≦25*	*25<*	0.37	(0.08–1.72)	0.21	0.44	(0.09–2.22)	0.32
Smoking	*No*	*Yes*	2.56	(0.75–8.76)	0.13	2.21	(0.46–10.61)	0.32
Hypertension	*No*	*Yes*	1.64	(0.43–6.20)	0.47	1.79	(0.44–7.36)	0.42
Hyperlipidemia	*No*	*Yes*	0.60	(0.18–2.06)	0.42	0.62	(0.15–2.44)	0.48
Diabetes	*No*	*Yes*	1.03	(0.22–4.83)	0.97	1.51	(0.29–7.86)	0.62
Hobby	*Yes*	*No*	6.54	(1.41–30.27)	0.02	6.74	(1.38–32.91)	0.02

CI, confidence interval

Discussion

Enjoying hobbies can improve quality of life by alleviating stress, improving daily activity, and normalizing automatic nervous system function. In the context of chronic life stress, an acute psychological challenge can provoke an exaggerated psychologic and sympathomedullary reactivity that is associated with decrements in individual natural killer cell function, and that persist beyond termination of the stressor and sympathomedullary recovery.[17] Mental stress cause an increase in platelet-dependent thrombin generation, which results in increased cardiovascular events.[18] However, the effect of enjoying hobbies on coronary function and cardiovascular prognosis has not yet been investigated. The association between endothelial dysfunction and the frequency of clinical events has been firmly established,[6,19] which is consistent with the present finding that the MACE ratio was significantly lower in the Normal ACh-responsive group than in the Poor ACh-responsive group.

Mechanisms by which hobbies may affect endothelial function

In this study, physical activities were among the variety of hobbies and cultural activities that were enjoyed by patients. The current concept of shear stress-induced changes in endothelial nitric oxide synthase (eNOS) expression/activity is based on cell culture experiments or animal models. For example, a significant increase in eNOS expression was observed in human umbilical vein endothelial cells and bovine arterial endothelial cells after 6 h of laminar shear stress.[20] Further, exercise training increases eNOS expression in coronary conduit and resistance vessels in animals.[21] In humans, exercise training can alleviate endothelial dysfunction in symptomatic patients with coronary artery disease by increasing eNOS activity and potentiating endothelium-dependent increase in blood flow in the context of exercise training.[22] Therefore, enjoying outdoor hobbies may improve cardiovascular outcomes by promoting coronary endothelial function.

One cohort study reported that people who rarely visited the cinema, concerts, museums, or art exhibitions had a higher mortality risk when compared with people who participated in these activities. Thus, attendance at various types of cultural events may have a beneficial effect on longevity.[23] Further, Takahashi and Matsushita[24] reported that music therapy once weekly over 2 years reduced systolic blood pressure, and reduced physical and mental stress in elderly patients suffering from moderate to severe dementia. Thus, enjoying indoor hobbies may also result in improved cardiovascular outcomes.

Relationship between lifestyle and mortality

Giltay et al.[25] reported that dispositional optimism is a relatively stable trait over 15 years, and is associated with a graded and inverse association with the risk of cardiovascular death in elderly men. Al-Khalili et al.[26] reported that important independent predictors of long-term all-cause mortality in middle-aged female patients surviving acute coronary syndrome included sedentary lifestyle, low physical exercise, and inadequate pulse rate and systolic blood pressure increase during exercise. In the present study, enjoying hobbies was the only predictor of MACE. Therefore, interventions to encourage enjoyable lifestyles during the early stage of atherosclerosis may result in improved cardiovascular outcomes.

Study limitations

This study has several notable limitations. For example, the proportion of patients who were taking ACE inhibitors or angiotensin II receptor blockers was greater in the Non-hobby group than in the Hobby group. Angiotensin-converting enzyme inhibitors increase systemic and coronary blood flow via an endothelial-dependent, bradykinin-mediated NO pathway.[27] However, ACh-induced percent change in coronary diameter and coronary blood flow were significantly greater in the Hobby group than in the Non-hobby group.

Further, detailed information regarding concomitant medication use was not available, and misclassification of both clinical and lifestyle exposures could have occurred due to measurement error or biological variation, because data were collected prospectively. However, such errors would probably be random with respect to the outcomes, and cause underestimation of the observed associations.

The present study also cannot distinguish between the widespread effects of lifestyles on cardiovascular prognosis and its effect on coronary endothelial function. Lifestyle habits could have been partially driven by changes in response to chronic disease development and physician guidance. Finally, the study population was relatively small, so larger trials are needed to determine the validity of these results.

Conclusion

In the early stage of arteriosclerosis, enjoying hobbies may improve cardiovascular outcomes via its favorable effects on coronary endothelial function.

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Relationship between hyperglycemia and coronary vascular resistance in non-diabetic patients

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Abstract

Background: Hyperglycemia upon hospital admission in patients with acute myocardial infarction is associated with the no-reflow phenomenon after successful reperfusion, and increased mortality. However, the mechanism underlying this phenomenon remains unclear. Therefore, the aim of this study was to characterize coronary hemodynamics in a homogenous group of non-diabetic patients without coronary artery disease.
Methods and Results: A total of 104 consecutive non-diabetic patients (mean age, 62±14 years) without coronary artery disease underwent Doppler flow study of the left anterior descending coronary artery. Vascular reactivity was examined by intra-coronary administration of papaverine, acetylcholine (Ach), and nitroglycerin using a Doppler guidewire. Coronary vascular resistance (CVR) was calculated as the mean arterial pressure divided by coronary blood flow (CBF). Baseline CVR was shown as CVR at control and minimal CVR was shown as CVR with papaverine administration. Fasting plasma glucose (FPG) level had a significant, positive correlation with baseline CVR and minimal CVR ($r=0.24$, $p<0.02$ and $r=0.21$, $p<0.05$, respectively). Hemoglobin A1c (HbA1c) also had a significant, positive correlation with baseline CVR and minimal CVR ($r=0.31$, $p<0.01$ and $r=0.32$, $p<0.01$, respectively). The percent change in CBF induced by Ach was inversely correlated with HbA1c but not with FPG ($r=0.22$, $p<0.05$ and $r=0.06$, $p=0.57$, respectively). By contrast, neither FPG nor HbA1c had significant correlation with coronary flow reserve to papaverine.
Conclusion: These data demonstrate that elevated glucose levels are associated with increases in baseline and minimal coronary vascular resistance. These changes may contribute to unfavorable coronary hemodynamics in non-diabetic patients without coronary heart disease.

Keywords: Coronary vascular resistance; FBS; HbA1; Hyperglycemia

1. Introduction

Hyperglycemia upon hospital admission in patients with acute myocardial infarction (AMI) is associated with the no-reflow phenomenon after successful reperfusion [1], resulting in larger infarct size and worse functional recovery. Further, hyperglycemia in patients with ST-segment elevation acute myocardial infarction is an important predictor of impaired epicardial flow before reperfusion therapy [2], and hyperglycemia in patients with AMI is associated with increased mortality [3–7]. However, the mechanisms underlying these adverse effects of hyperglycemia remain unknown. Therefore, the aim of this study was to characterize coronary hemodynamics in a

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Table 1
Clinical characteristics of the study patients.

Age (years)	62±14 (17–85)
Male gender	69 (66%)
Risk factors	
Hypertension	57 (55%)
Hyperlipidemia	35 (34%)
Smoker	27 (26%)
Laboratory data	
FPG (mg/dl)	94±8 (74–120)
HbAlc (%)	5.2±0.4 (4.1–6.3)
Total-cholesterol (mg/dl)	197±37 (114–314)
Triglycerides (mg/dl)	122±64 (40–368)
HDL-cholesterol (mg/dl)	57±15 (28–98)
LDL-cholesterol (mg/dl)	113±28 (53–211)

HDL: high density lipoprotein; LDL: low density lipoprotein; Values are mean±SD.

homogenous group of non-diabetic patients without coronary artery disease.

2. Methods

2.1. Study population

A total of 187 consecutive non-diabetic patients who had been referred for cardiac catheterization to exclude coronary artery disease were considered for enrollment in this study. Of these, 104 patients met the following inclusion criteria: 1) angiographically smooth arteries; 2) mild irregularities, <30% lumen diameter stenosis by visual assessment in any major conduit vessel; 3) proximal coronary arteries >2.0 mm in diameter; and 4) lacking a history of previous myocardial infarction, previous coronary revascularization, valvular heart disease, variant angina, cardiomyopathy, or myocarditis.

Patients meeting the following criteria were considered to have obvious diabetes and excluded: 1) previous diagnosis of diabetes, 2) current treatment by oral hypoglycemic agents or insulin, or 3) concentration of fasting plasma glucose (FPG) >126 mg/dl or hemoglobin A1c (HbA1c) >6.5% at admission [8].

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a *priori* approval by the institution's human research committee.

2.2. Study protocol

Diagnostic coronary angiography was performed using a 6F Judkins catheter with a standard femoral percutaneous approach. Heparin (5000 units) was administered at the beginning of the procedure. Non-ionic contrast material was used for all patients. No nitroglycerin was given prior to the diagnostic procedure. Coronary blood flow (CBF) response to papaverine, acetylcholine (Ach), and nitroglycerin was studied according to previous reports [9,10]. After control coronary angiograms, interventions were performed as follows: 1) a 0.014-inch Doppler guidewire (Cardiometrics, Santa Anna, CA, USA) was introduced into the left anterior descending coronary artery; 2) after obtaining a stable Doppler signal, a bolus of papaverine (an endothelium-independent vasodilator in resistance coronary arteries) (12.5 mg/5 ml) was injected through a catheter; 3) infusion of Ach (an endothelium-dependent vasodilator in resistance and conduit coronary arteries) (0.5 ml/min) at a dose of 3 µg/min for 2 min was performed via the catheter [11,12,4] a bolus of nitroglycerin (an endothelium-independent vasodilator in conduit coronary arteries) (200 µg/5 ml) was administered. Drugs were infused with a minimum 5-min interval. Coronary arteriography was performed before and 2 min after each dose of Ach and after administration of nitroglycerin. Phasic CBF velocities, arterial blood pressure, and heart rate were monitored continuously and recorded. Measurements obtained during steady state conditions were used as control values for later analysis.

Doppler flow velocity spectra were analyzed on-line to determine time-averaged peak velocity. Volumetric CBF was determined from the formula: CBF = cross-sectional area × average peak velocity × 0.5 [13]. Coronary flow reserve to papaverine was calculated as the ratio of maximal CBF induced by papaverine to basal CBF, which was equivalent to

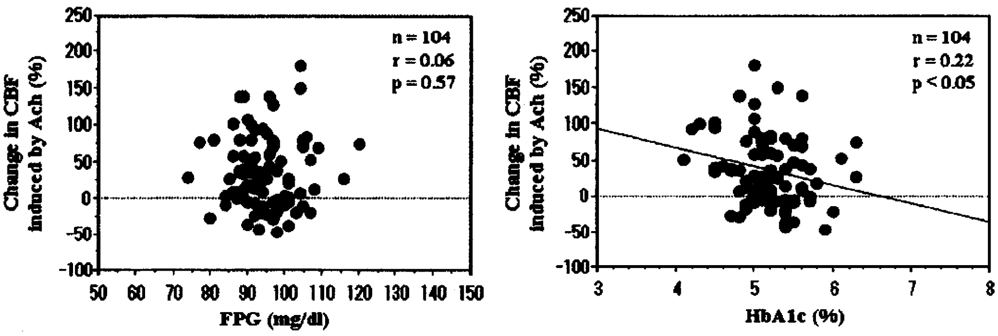

Fig. 1. Scattergram illustrating the correlation between percent change in CBF induced by Ach and FPG (left panel) and HbA1c (right panel).

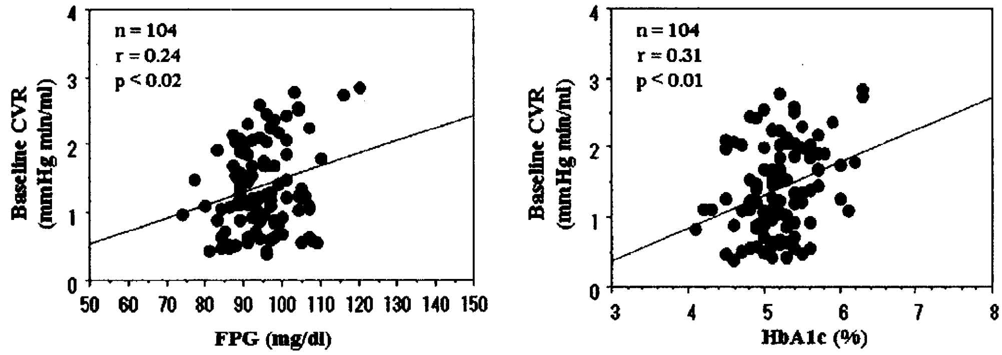

Fig. 2. Scattergram illustrating the correlation between baseline CVR and FPG (left panel) and HbA1c (right panel).

the endothelium-independent function of the resistance coronary artery. Endothelium-dependent function was calculated as the percent increase of CBF in response to Ach [9,14].

Coronary vascular resistance (CVR) was calculated by mean arterial pressure divided by CBF. Baseline CVR is shown as CVR at control, and minimal CVR is shown as CVR with papaverine administration.

2.3. Statistics

All data are expressed as the mean value±SD. One-way analysis of variance (ANOVA) was used for comparison of continuous variables, and significance of difference was calculated using the Scheffe F test. Differences were considered significant at $p<0.05$. Statistical analysis was performed with Statview, ver. 5.0 (SAS Institute Inc., Cary, NC).

3. Results

A total of 104 patients were evaluated. Patient characteristics are shown in Table 1. All patients enrolled in this study had concentrations of FPG< 126 mg/dl and HbA1c<6.5%.

3.1. Changes in coronary blood flow

The relationship between FPG, HbA1c, and percent change in CBF induced by Ach are shown in Fig. 1. Percent change in CBF induced by Ach (i.e., namely endothelium-dependent vasodilatation in resistance arteries) was inversely correlated with HbA1c but not with FPG, which suggests that chronically higher levels of glucose concentration are associated with impaired endothelial function in resistance coronary arteries in non-diabetic patients. Coronary flow reserve to papaverine (i.e., endothelium-independent vasodilatation in resistance arteries) did not correlate with FPG or HbA1c ($r=0.08$, $p=0.42$; $r=0.02$, $p=0.85$, respectively) in non-diabetic patients.

3.2. Changes in coronary artery diameter

Neither FPG nor HbA1c was correlated with percent change in coronary artery diameter (CAD) induced by Ach (i.e., namely endothelium-dependent vasodilatation in epicardial arteries) ($r=0.01$, $p=0.97$ and $r=0.03$, $p=0.82$, respectively). Similarly, percent change in CAD induced by nitroglycerin (i.e., namely endothelium-independent vasodilatation in epicardial arteries) did not correlate with FPG or HbA1c ($r=0.01$, $p=0.94$ and $r=0.06$, $p=0.57$, respectively). Thus, neither FPG nor HbA1c were correlated with endothelium-dependent and -independent vasodilation of the epicardial coronary arteries in non-diabetic patients.

3.3. Coronary vascular resistance

The relationship between baseline CVR and minimal CVR to FPG and HbA1c are shown in Figs. 2 and 3, respectively.

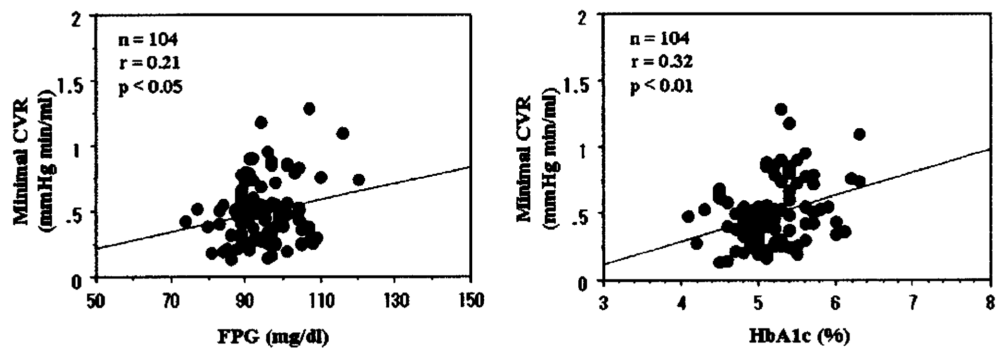

Fig. 3. Scattergram illustrating the correlation between minimal CVR and FPG (left panel) and HbA1c (right panel).

FPG and HbA1 had a significant, positive correlation with baseline CVR and minimal CVR. These results suggest that acute and chronic high glucose concentrations are associated with increased vascular resistance in coronary arteries at baseline and at a hyperemic state in non-diabetic patients.

4. Discussion

The present study demonstrated that chronic exposure to high glucose concentrations is associated with coronary endothelial dysfunction and that baseline and minimal CVR are elevated in the context of acute and chronic hyperglycemia in non-diabetic patients without coronary artery disease. These data suggest that elevated blood glucose concentrations may contribute to impaired coronary flow in non-diabetic patients.

4.1. Hyperglycemia and coronary endothelial function

Previous studies have reported that chronic hyperglycemia results in impairments in endothelium-dependent coronary artery vasodilation [15,16], which is consistent with results from the present study. Further, other studies have demonstrated that acute hyperglycemia results in impaired coronary flow via attenuation of mitochondrial ATP—sensitive potassium channel (K_{ATP} channel) activation and via promotion of platelet-dependent thrombus formation [17,18]. By contrast, other investigators have reported that hyperglycemia-induced vascular damage is mediated by increased production of oxygen free radicals, including superoxide anion, from endothelial cells [19–21]. Increased superoxide anion can inactivate nitric oxide and result in enhanced contractility and proliferation of vascular smooth muscle cells with increased vasomotor tone, platelet hyper-reactivity [22], alteration of the adhesive properties of the endothelium [23], and increased production of cytokines [24].

4.2. Hyperglycemia and coronary vascular resistance

Farouque et al. [25] suggested that K_{ATP} channels contribute to basal CVR by demonstrating that inhibition of these channels resulted in impairments in resting CVR. Further, acute hyperglycemia prevents the positive effect of ischemic preconditioning, probably through the attenuation of mitochondrial K_{ATP} channel activity. Barbagallo et al. [26] reported that glucose increased intracellular calcium content in vascular smooth muscle, while other investigators reported that FPG and HbA1c levels are both closely related to fasting basal cytosolic free calcium levels [27]. These observations are consistent with results from the present study and may provide a mechanistic link between why acute hyperglycemia and impaired coronary flow.

In this study, patients with obvious diabetes were excluded. Kawano et al. [28] demonstrated glucose-induced impairments in endothelium-dependent vasodilation in patients with IGT, even when FRG levels were within a normal limit. Further, this effect persisted at 2 h after glucose loading. Thus, repeated exposure to postprandial hyperglycemia may play an important role in the vascular dysfunction, even in our patients without obvious diabetes.

4.3. Limitations

This study possesses several limitations. First, the study population included only patients with normal or mildly diseased coronary arteries. Thus, the present findings may not be applicable to patients with advanced coronary artery disease. Second, the present study was based on a retrospective analysis of the patients and was only a descriptive study in which we established an association between elevated blood glucose concentrations and an increase of CVR; a more prospective study is required to determine the effect of glycemic control on CVR.

5. Conclusion

Increases in baseline and minimal CVR in association with acute or chronic hyperglycemia may contribute to unfavorable coronary hemodynamics and mortality in non-diabetic patients.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [29].

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