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Ambulatory and Silent Myocardial Ischemia in Women with Coronary Microvascular Dysfunction: Results from the Cardiac Autonomic Nervous System Study (CANS)

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Abstract

Background: Up to two-thirds of patients with obstructive coronary artery disease (CAD) have silent ischemia (SI), which predicts an adverse prognosis and can be a treatment target in obstructive CAD. Over 50% of women with ischemia and no obstructive CAD have coronary microvascular dysfunction (CMD), which is associated with adverse cardiovascular outcomes. We aimed to investigate the prevalence of SI in CMD in order to consider it as a potential treatment target.

Methods: 36 women with CMD by coronary reactivity testing and 16 age matched reference subjects underwent 24-hr 12-lead ambulatory ECG monitoring (Mortara Instruments) after anti-ischemia medication withdrawal. Ambulatory ECG recordings were reviewed by two-physician consensus masked to subject status for SI measured by evidence of ≥ 1 minute horizontal or downsloping ST segment depression ≥ 1.0 mm, measured 80 ms from the J point.

Results: Demographics, resting heart rate, and systolic blood pressure were similar between CMD and reference subjects. Thirty-nine percent of CMD women had a total of 26 SI episodes vs. 0 episodes in the reference group (p=0.002). Among these women 13/14 (93%) had SI, and few episodes (3/26, 12%) were symptomatic. Mean HR at the onset of SI was 96±13 bpm and increased to 117±16 bpm during the ischemic episodes. 87% reported symptoms that were not associated with ST depressions.

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Conclusions: Ambulatory ischemia is prevalent in women with CMD, with a majority being SI, while most reported symptoms were not accompanied by ambulatory ischemia. Clinical trials evaluating anti-ischemic medications should be considered in the CMD population.

Keywords

coronary vascular dysfunction; silent ischemia; ambulatory monitoring

Background:

Nearly half of women who undergo coronary angiography for symptoms of myocardial ischemia have no obstructive coronary artery disease (CAD) defined as ≥ 50% stenosis of an epicardial coronary artery. [1, 2] Patients with evidence of ischemia and no obstructive coronary artery disease (INOCA) are increasingly recognized with an estimated prevalence of 3–4 million in United States.[3] Current evidence identifies these women at significant risk for adverse cardiovascular events.[1, 2, 4–6] Coronary microvascular dysfunction (CMD), from endothelium dependent or independent mechanisms, leads to abnormal myocardial blood flow regulation and may contribute to ischemia in this population.[3, 5, 7, 8] CMD is highly prevalent in patients with INOCA, and may be a treatment target, but therapeutic strategies are not well established.

Myocardial ischemia can present with angina or angina equivalents; however, ischemia can also occur in the absence of symptoms, known as silent ischemia (SI). SI is prevalent in as many as two-thirds of obstructive CAD patients, often at relatively low heart rates of 90–120 beats per minute.[9, 10] SI on ambulatory ECG monitoring is associated with adverse cardiovascular outcomes including death,[10–12] and anti-ischemic therapy directed at SI improves outcomes in obstructive CAD subjects.[13, 14] However, the relationship between CMD and SI has not been well characterized in contemporary, well-characterized subjects. [15, 16] Given that treatment of CMD to reduce event rates is not established, we aimed to investigate the prevalence of SI in CMD in order to consider treatment of SI with anti-ischemic therapy as a potential treatment target for CMD.

Methods:

Study Subjects

Subjects were recruited from the Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) Study (PI: Bairey Merz), which aims to study the pathophysiology of women with signs and symptoms of ischemia but no obstructive CAD on angiography.[17, 18] As part of the WISE-CVD study, subjects underwent invasive coronary reactivity testing (CRT) to diagnose CMD as previously published.[5, 8, 19] Women with CMD from the WISE-CVD study were retrospectively enrolled in the NHLBI-sponsored Cardiac Autonomic Nervous System (CANS) sub-study (n=36) if they agreed to further testing in the CANS study. CMD subjects were compared to age matched asymptomatic reference subjects (n=16), recruited for WISE-CVD cardiac magnetic resonance imaging purposes.[8] Inclusion and exclusion criteria for CANS were identical to WISE-CVD, which has been previously published.[5, 8, 17, 20] In addition to baseline characteristics, clinical, and

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medication history, the Seattle Angina Questionnaire (SAQ) was collected.[21] The reference subjects were asymptomatic individuals with no cardiac risk factors, not on any cardiac medications, and who had a normal exercise treadmill testing. These WISE-CVD and CANS projects were approved by the Institutional Review Board at Cedars-Sinai Medical Center.

Coronary Reactivity Testing Protocol

Coronary reactivity testing (CRT) protocol has been previously published.[19] In brief, coronary functional testing was done using intracoronary adenosine, acetylcholine, and nitroglycerin.[19] After placement of a Doppler wire (FloWire®, Volcano Corp), in the left anterior descending coronary artery, coronary flow reserve (CFR) to adenosine (18 mcg and 36 mcg) was measured as the ratio of the hyperemic average peak velocity to baseline average peak velocity, and CFR ≤ 2.5 was considered abnormal. Graded intracoronary infusions of acetylcholine (0.364 mcg and 36.4 mcg) were used to asses coronary artery diameter change, and ≤ 5% dilation measured by quantitative coronary angiography was considered abnormal. Coronary blood flow change in response to acetylcholine was calculated as previously published, and change ≤ 50% was abnormal.[19] Smooth muscle function was assessed using intracoronary nitroglycerin (200 mcg), with change < 20% was abnormal.

Assessment of Ambulatory ECG Recordings

Participants in the study were monitored by 12-lead 24-hr ambulatory ECG (AECG) (Mortara Instruments®) and were instructed to keep a journal of chest pain or chest pain equivalents while monitored. Medications were held for 24 hours prior to AECG monitoring and during the monitoring period. Long acting calcium channel blockers and nitrates were withheld for 48 hours prior to start of AECG. A trained and experienced technician processed the AECG recordings. A recording was considered eligible if the following criteria were met: over 12 hours of analyzable data, both daytime and nighttime periods available, and sinus rhythm.[20] Tracings were reviewed by two physicians masked to clinical information, for evidence of ≥ 1 minute horizontal or down sloping ST segment depression ≥ 1.0 mm, measured 80 ms from the J point. During the 24-hr monitoring subjects were asked to note the time of onset and duration, and describe the symptoms in a diary log. Subject journals were then evaluated to see if symptoms of angina occurred at or near the time of each episode.

Statistical Analysis

Case control analysis was performed using Fisher’s exact test and the Kruskal-Wallis test for categorical and quantitative variables, respectively. Data is presented as n (%) or mean ± SD. Statistically significant values are considered when $p \leq 0.05$.

Results

Table 1 compares the women with CMD (n=36) with age matched reference subjects (n=16). Overall, no significant hemodynamic differences were noted other than those with CMD were found to have lower diastolic blood pressures than reference subjects. Over a third of CMD subjects had hypertension and hyperlipidemia, with approximately 10% with diabetes.

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CMD subjects were more likely to be on aspirin, statins, nitrates, ACE-I, calcium channel blockers and beta blockers than reference subjects as expected due to study design. The mean time between CRT and AECG monitoring was 2.6 ± 1.9 years.

Silent Ischemia on Ambulatory Monitoring

In the CMD group, 39% (14/36) had at least one episode of ST depression on ambulatory monitoring compared to 0 subjects in the reference group (p=0.002). Among CMD subjects, we compared those with ambulatory ischemia to those without ambulatory ischemic ST depressions, and found no differences in clinical characteristics (Table 2). There were a total of 26 episodes of ST depressions in 14 CMD subjects. Only three (12%) of these episodes of ST depressions were symptomatic when time periods of ischemic ST depressions were compared to angina or angina-equivalents reported in subject diaries. A total of 23 SI episodes were recorded in 13 CMD subjects (Figure). One CMD subject had 4 episodes of chest pain, and only one was associated with ST depressions. Another CMD subject had 4 episodes of ST depressions, of which 2 were symptomatic and 2 were SI. Three out of 23 SI episodes (13%) were during nighttime (10 PM to 6 AM). The distribution of SI episodes largely favored inferior leads (II, III, or aVF) with 87% of the episodes involving these leads. The mean heart rate (HR) at onset of SI was found to be 96±13 bpm and the mean peak HR was 117±16 bpm. The mean difference of HR change from prior to SI episode to peak HR during SI was 21±15 bpm. 61% of SI episodes occurred at HR < 100 bpm prior to the onset of SI episode. There was a trend of more SI episodes at peak HR >120 bpm compared to ≤ 120 bpm (p=0.06). There were no differences in the number of ischemic episodes that occurred with a heart rate change of ≥20 bpm or <20 bpm. A majority of episodes occurred with a change of HR less than 30 bpm from baseline.

CRT Results and Ambulatory Ischemia

There were no differences in CRT measures comparing those with ambulatory ischemia (n=14) vs. those without ambulatory ischemia (n=22): (a) coronary flow reserve to adenosine: 2.88±0.97 vs. 2.67±0.63 (p=0.9); (b) % Δ coronary diameter to acetylcholine: −6.9±21.4 vs. −1.4±18.8 (p=0.3); (c) % Δ coronary blood flow to acetylcholine: 72.2±103.5 vs. 81.0±81.9 (p=0.5); (d) %Δ coronary diameter to nitroglycerin: 18.4±10.6 vs. 11.6±15.5 (p=0.1). There were also no differences in CRT measures between SI vs. non-SI group. Those with ≥ 2 CRT abnormalities (n=11) did not have more SI episodes compared to those with <2 abnormal CRT pathways (n=3) (p= 0.30).

Symptom Burden

Among the CMD women, 15 out of 36 (42%) reported angina symptoms such as chest pressure, dyspnea, or lightheadedness in their symptom diaries during 24-hour monitoring. Among those who reported angina, 13 (87%) reported symptoms that were not associated with ST depressions during the 24 hours of ambulatory monitoring. CMD subjects had a high symptom burden as determined by the five subscales of the SAQ (mean ± SD): (a) physical limitation: 75.0±20.7; (b) angina stability: 56.9±24.4; (c) angina frequency: 62.5±26.4; (d) treatment satisfaction: 87.3±15.3; and (e) quality of life: 64.8±23.6. There was no difference in the SAQ scores between those with and without ambulatory ischemia in

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all five SAQ domains. There were no differences in SAQ measures between SI vs. non-SI group.

Discussion

To our knowledge, this is the first report on prevalence of SI in a population of women who have undergone CRT to diagnose CMD. We demonstrate that ambulatory ischemia detected by ST segment depressions on 24-hour AECG monitoring is prevalent in over one-third of women with CMD compared to matched reference subjects. Furthermore, a majority of these ST depressions are SI and occurred during the daytime. CMD women in this study demonstrated a high burden of angina, consistent with prior reports.[22, 23] While over a third of CMD subjects reported symptoms during 24-hour period, their symptom experience was not associated with ST segment depressions in a majority of cases. Specific CRT measures were not different among those with vs. without SI.

We have previously documented objective evidence of myocardial ischemia in a similar cohort of patients, by phosphorus cardiac magnetic resonance spectroscopy.[24] We have also documented an almost 8% myocardial scar in CMD population, detected by cardiac MRI late gadolinium enhancement (LGE), and approximately 1% annual new LGE in women with CMD, the majority of whom do not have a clinical history of myocardial infarction.[25] Our finding of a high prevalence of ambulatory ischemia and specifically SI extends these findings and support further investigation into understanding mechanistic pathways in order to develop treatment targets. Recurrent episodes of ischemia have been demonstrated via biopsy to be associated with anatomic changes including myocardial cellular degeneration, increased fibrosis, and hypertrophy.[26, 27] These anatomic changes, in addition to the ischemic events, are likely contributing factors to the increased rates of fatal arrhythmias noted in individuals with SI.[28]

Interestingly, nearly two-thirds of SI episodes in CMD subjects occurred at heart rates less than 100 bpm prior to the onset of ST segment depression. The mean resting HR in the CMD group increased approximately 20 bpm prior to the onset of SI; therefore, it is possible that demand related ischemia may be the explanation of ST segment depression. Our observed heart rate range for SI in CMD is comparable to prior reports in the obstructive CAD and previously termed “cardiac syndrome X” (CSX) populations.[9, 29, 30]

Historical CSX literature has described prevalent ambulatory ischemia that is dominantly SI and occurs at relatively low heart rates. [31–33] In a study looking at autonomic nervous system dysfunction, 14 (61%) out of 23 patients with CSX had 1 or more episodes of ST depression in 24-hour monitoring. Only one of the 14 subjects had chest pain during the transient ST segment depression.[15] CSX described in the literature included heterogeneous groups with chest pain and no obstructive CAD who may or may not have had CMD, because no objective measures of coronary flow reserve or endothelial function were obtained.[34] Our results extend prior findings in CSX population to a rigorously defined cohort of women with CMD. Further, our reference control subject comparison confirms these are not false positive ECG findings, and questions prior reports of false positives in population studies not densely phenotyped.

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Prior work in obstructive CAD has demonstrated that ischemic episodes on ambulatory monitoring independently predict adverse outcomes.[12, 35–37] In 107 patients with chronic stable angina, the 46 (43%) subjects with one or more episode of SI were found to have a threefold increase in risk of cardiac death in the two year follow up period compared to those with no SI (24% vs. 8%, p=0.023).[11] However, adverse outcomes from SI has not previously been investigated in CMD subjects diagnosed by comprehensive CRT.

Our current results also demonstrate that the CMD subjects have a high burden of chest pain which appears to be independent of ambulatory ischemia. The mechanisms contributing to cardiac pain are multi-factorial and complex.[38] Patients with CMD have heightened nociception, evidenced by a higher pain sensitivity and perception with contrast injection in the catheterization lab, during right ventricular pacing, and during adenosine infusion.[39, 40] Cerebral cortical dysfunction and abnormal neural processing has also been suggested in SI.[23] In a study of non-diabetic patients with exercise induced ischemia, less cortical activation was found in asymptomatic patients compared to symptomatic patients with angina.[23] Rosen et al have reported brain activation in regions such as the prefrontal cortex and the left inferior anterior cingulate during angina in patients with CAD.[23, 41] In contrast, in those with silent ischemia there was a failure of frontal cortex activation, although there was thalamic activation (similarly to the angina group).[41] They concluded that abnormal CNS processing of afferent pain signals from the heart may be playing a role in SI.[23] Chemical substances such as adenosine and dipyridamole mediate chest pain but failed to induce electrographic ischemic changes.[10, 42, 43]

Mechanical stretching of the coronary arteries is also proposed as a mechanism supported by observations that some individuals experience pain with higher balloon inflation pressure during percutaneous transluminal coronary angioplasty (PTCA).[10, 44] In addition to autonomic neuropathy, several biomarkers have also been associated with SI. Beta-endorphins, peripheral benzodiazepine receptors and anti-inflammatory cytokines are increased in patients with SI compared to symptomatic counterparts.[22, 45–47] Clearly, more investigation in the brain-heart axis and contributions to angina and SI in CMD population is needed.

While we note a high prevalence of SI in CMD, whether treatment of SI in the CMD population would lead to improved outcomes is yet to be determined. SI has been used as a treatment target in several ischemic heart disease studies, such as the Atenolol Silent Ischemia Study (ASIST) randomized individuals with a history of SI to atenolol vs. placebo.[49] The atenolol group demonstrated a significant decrease in primary outcomes including MI, arrhythmias, and death compared to the placebo group,[49] which was accompanied by a significant decrease in episodes of SI ($p < 0.001$).[49] In the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, three groups with SI were compared: angina-guided therapies, ischemia-guided therapies, and revascularization.[50] A graded reduction in adverse cardiovascular outcomes and episodes of ischemia were observed (0% in revascularization, 1.6% ischemia-guided, and 4.4% angina-guided, p=0.004).[50] The Total Ischemic Burden Bisoprolol Study (TIBBS) found that individuals treated to 100% resolution of their ischemic episodes had fewer adverse outcomes as compared to those with residual episodes (17.5% vs. 32.3%, p=0.008).[50]

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Study Limitations.

Our relatively small sample size of cases and reference subjects prevents us from making any conclusions about whether specific endothelium-dependent or independent vasomotor pathways are associated with more SI. Additionally, while medications were withdrawn during ambulatory monitoring, our patients had been treated on anti-ischemic, anti-anginal medications prior to their inclusion in this study, and thus represent a "treated" population which may underestimate SI prevalence. There is also the concern that withdrawal of medications for AECG monitoring may enhance ischemia, which could influence AECG results in our CMD group. We also did not systematically collect information on conditions that impact heart rates and ST segment changes, such as sleep, physical, and mental activity. This study was strengthened by the inclusion of women with objective evidence of CMD diagnosed by CRT in the setting of no obstructive CAD.

Conclusions:

Our results demonstrate that over one-third of women with CMD have SI detected by ambulatory monitoring, while conversely most angina is not related to ambulatory ischemia, both similar to obstructive CAD findings. Given the previously established adverse prognostic significance of SI in obstructive CAD, and the poor outcomes associated with CMD, clinical trials evaluating anti-ischemic medications should be considered in the CMD population. Future studies need to target longer duration of ambulatory monitoring to detect SI burden in women with CMD and its relation to adverse cardiovascular outcomes.

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Highlights:

1. Silent ischemia (SI) is prevalent in women with coronary microvascular dysfunction (CMD) compared to reference controls.
2. SI occurs in CMD at heart rates similar to obstructive CAD population.
3. Symptoms of CMD were not accompanied by ambulatory ischemia.
4. Treatment of SI with anti-ischemic therapy could be a potential treatment for CMD.

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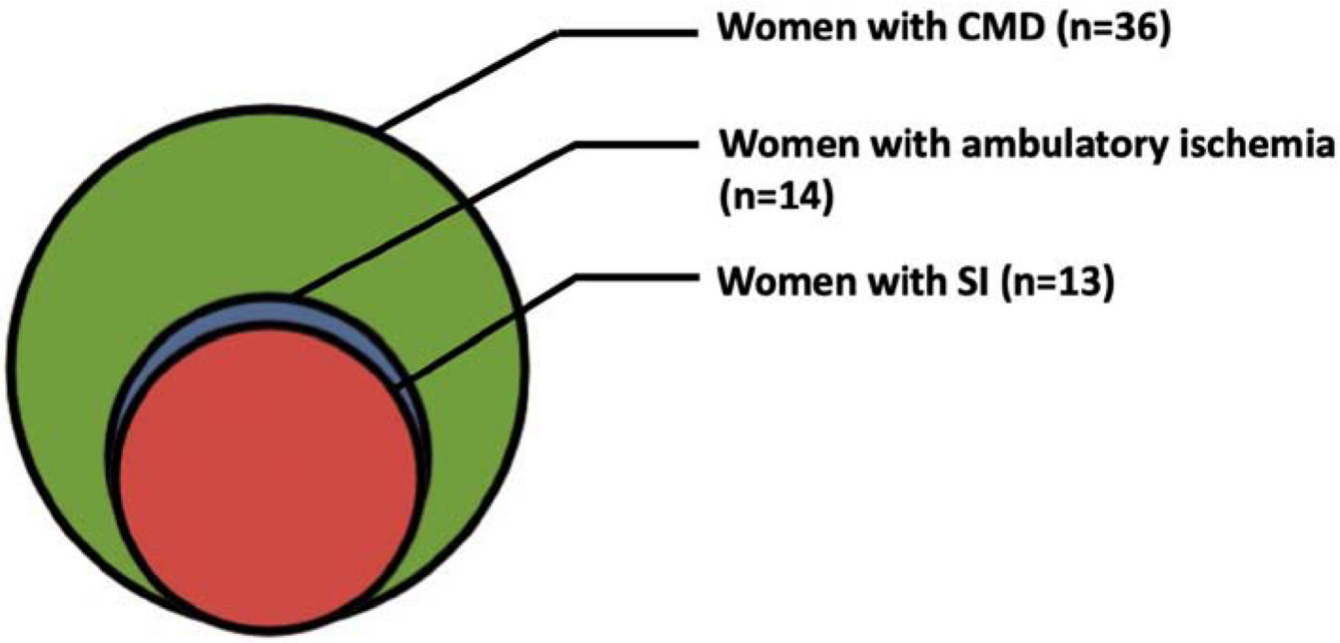

Figure :

Silent ischemia is highly prevalent in women with coronary microvascular dysfunction despite having no obstructive epicardial coronary artery stenosis. CMD = Coronary microvascular dysfunction, SI = Silent ischemia

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Table 1:

Comparison of CMD and Reference Subjects

Characteristic	CMD Subjects (n=36)	Reference Subjects (n=16)	p-Value
Age	57± 10	51± 20	0.8
Body Mass Index	27± 6	26 ± 4	0.7
Systolic Blood Pressure (mmHg)	118 ± 15	122 ± 16	0.3
Diastolic Blood Pressure (mmHg)	62 ± 8	68 ± 8	0.02
Heart Rate (bpm)	68 ± 12	65 ± 12	0.5
Hypertension	13 (36%)	0 (0%)	0.005
Diabetes Mellitus	4 (11%)	0 (0%)	0.3
Hyperlipidemia	14 (39%)	0 (0%)	0.002
Prior Tobacco Use	9 (25%)	0 (0%)	0.04
Statin	24 (67%)	0 (0%)	<0.001
Angiotensin Converting Enzyme Inhibitor (ACE-I)	9 (25%)	0 (0%)	0.05
Angiotensin Receptor Blocker	5 (14%)	0 (0%)	0.3
Aspirin	27 (75%)	1 (7%)	<0.001
Beta Blocker	15 (42%)	0 (0%)	0.004
Calcium Channel Blocker	10 (28%)	0 (0%)	0.05
Nitrate	21 (58%)	0 (0%)	<0.001
Ranolazine	8 (22%)	0 (0%)	0.2
Hormone Therapy	8 (22%)	3 (19%)	>0.9
Ambulatory Ischemia*	14 (39%)	0 (0%)	0.002
Silent Ischemia^	13 (36%)	0 (0%)	0.005

*Defined as evidence of ≥ 1 minute horizontal or downsloping ST segment depression ≥ 1.0 mm, measured 80 ms from the J point on ambulatory monitoring; CMD = coronary microvascular dysfunction

^Among those with ambulatory ischemia, the absence of chest pain or chest pain equivalents.

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Table 2:

Comparison of CMD subjects Stratified by Ambulatory Ischemia

Characteristics	Ambulatory ST Depressions (14)**	No ST Depressions (22)	p-value
Age (years)	59±7	56±11	0.3
Body Mass Index	27±5	27±6	0.9
Systolic Blood Pressure (mmHg)	119±16	118±15	0.9
Diastolic Blood Pressure (mmHg)	61±8	62±8	0.6
Heart Rate (bpm)	63±8	70±13	0.2
Hypertension	4 (29%)	9 (41%)	0.5
Diabetes Mellitus	1 (7%)	3 (14%)	>0.9
Hyperlipidemia	5 (36%)	9 (41%)	>0.9
Tobacco Use	6 (43%)	3 (14%)	0.1
Statin	11 (79%)	13 (59%)	0.3
ACE-I	6 (43%)	3 (14%)	0.1
Angiotensin Receptor Blocker	1 (7%)	4 (18%)	0.6
Aspirin	10 (71%)	17 (77%)	0.7
Beta Blocker	6 (43%)	9 (41%)	>0.9
Calcium Channel Blocker	2 (14%)	8 (36%)	0.3
Nitrate	10 (71%)	11 (50%)	0.3
Ranolazine	1 (7%)	7 (32%)	0.1
Hormone Therapy	4 (29%)	4 (18%)	0.7

** Includes SI and non-SI subjects.

CMD = coronary microvascular dysfunction