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ESC: Evidence Grows for HFpEF as Microvascular Disease

— Studies on exact mechanisms, potential targets still needed

by Nicole Lou, Contributing Writer, MedPage Today

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MUNICH -- Coronary microvascular dysfunction (CMD) was highly prevalent in heart failure with preserved ejection fraction (HFpEF), according to an echocardiographic study. The findings add to growing evidence that CMD could be targeted for HFpEF therapy.

Defined as coronary flow reserve (CFR) <2.5 by transthoracic Doppler echocardiography, CMD was observed in 75% of the 202 HFpEF patients included in the prospective PROMIS-HFpEF study conducted in Sweden, U.S., Finland, and Singapore. These CMD patients had a mean CFR of 2.13 (median 2.08), according to a presentation by Carolyn Lam, MBBS, PhD, of National Heart Centre Singapore & Duke-National University of Singapore.

She reported at a late-breaking trial session at the European Society of Cardiology annual meeting here that, after multivariable adjustment, worse CFR was tied to:

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- Systemic endothelial dysfunction as indicated by higher urinary albumin-to-creatinine ratio (β coefficient=4.1, 95% CI 2.7-6.7, *P*=0.028) and lower reactive hyperemia index (β coefficient=-0.11, 95% CI -0.21 to 0.00, *P*=0.041)
- More severe HF as indicated by higher NTproBNP levels (β coefficient=543, 95% CI 132-954, *P*=0.010)
- Cardiac dysfunction as indicated by lower tricuspid annular plane systolic excursion (β coefficient=-0.52, 95% CI -1.03 to -0.02, *P*=0.042) and lower right ventricular free wall strain (β coefficient -0.50, 95% CI -1.5 to -0.1, *P*=0.022)

Results from PROMIS-HFpEF (PRevalence Of MIcrovascular dySfunction in Heart Failure with Preserved Ejection Fraction) were also published online in *European Heart Journal*.

"Microvascular dysfunction may be a promising composite risk marker and therapeutic target in HFpEF," Lam's group suggested, noting that until now, evidence of CMD in HFpEF has been small and indirect.

"The PROMIS-HFpEF study comes at a critical juncture to address key knowledge gaps that adversely impact women, the majority of CMD and HFpEF victims; indeed, 55% of the study sample are women," noted C. Noel Bairey Merz, MD, of Cedars-Sinai Smidt Heart Institute in Los Angeles, and colleagues in an accompanying editorial.

This group called the data "some of the strongest evidence to date of a CMD-HFpEF relationship" but commented that exactly how CMD-related ischemic damage contributes to HFpEF remains an "important knowledge gap."

Even so, the study "gives us a different target in a field that's been very disappointing," said Ileana Piña, MD, MPH, of Montefiore Medical Center in New York City, in an interview. "The concept is that HFpEF is not just one disease. We keep thinking as if it were just one disease, [but] we're coming to the realization it's probably several syndromes, and maybe the end results are the same but how they get there is different."

"The common theme is we need to start thinking about other targets of drugs," Piña emphasized in anticipation of future controlled trials with outcomes data.

All patients in the study got two-dimensional echocardiography with Doppler and tissue

Doppler imaging. Analyses were performed after adjusting for factors such as age, sex, BMI, and the fact that those who had CMD were more likely to have atrial fibrillation (58% versus 25% for those without CMD, *P*=0.004) and a history of smoking (70% versus 43%, *P*=0.0006). Patients with unrevascularized macrovascular CAD were excluded.

Notably, 25% of study participants did not show evidence of CMD. This may be due to HFpEF being a heterogeneous syndrome giving patients a more "extra-cardiac" cause of fluid, Lam and colleagues suggested, another possibility being that other factors besides endothelial dysfunction are the cause of the HFpEF syndrome in these individuals.

Bairey Merz and colleagues suggested that next steps should include cardiac MRI and MR spectroscopy studies to elucidate the specific mechanisms linking CMD-related myocardial ischemia, myocellular damage, and HFpEF; improving HFpEF subgroup phenotyping; and identifying new treatment targets.

"Only then can mechanistically supported HFpEF intervention trials be considered," they said, with potential candidates such as anti-ischemic/scar, strain/remodeling, and anti-fibrotic therapies.

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