Pengaruh External Counterpulsation (ECP) terhadap Vascular Endothelial Growth Factor-A (VEGF-A) dan Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2), serta hubungannya dengan micro ribonucleic acid 92a (miR-92a) pada Pasien Penyakit Jantung Koroner = The effect of External Counterpulsation (ECP) on Vascular Endothelial Growth Factor-A (VEGF-A) and Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2), and its relationship with micro ribonucleic acid 92a (miR-92a) in Coronary Artery Disease Patients

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Abstrak

Latar Belakang: ECP mampu menurunkan frekuensi angina, meningkatkan kualitas hidup, serta memperbaiki exercise–induced ischemia time. Manfaat tersebut dapat bertahan beberapa tahun setelah ECP. Mekanisme manfaat jangka panjang ECP tersebut telah dibuktikan akibat adanya angiogenesis yang diduga diperankan VEGF-A, VEGFR-2, dan miR-92a.

Tujuan: Mengetahui efek ECP terhadap VEGF-A dan VEGFR-2, serta hubungannya dengan miR-92a pada pasien angina refrakter.

Metode: Studi ini merupakan uji klinis acak tersamar ganda yang melibatkan 50 subjek dengan angina refrakter. Subjek dirandomisasi (1:1) ke dalam kelompok terapi ECP atau sham, yang masing-masing dilakukan selama 1 jam, hingga 35 kali. Kadar VEGF-A, VEGFR-2, dan miR-92a plasma diukur sebelum dan sesudah terapi menggunakan metode enzyme-linked immunosorbent assay (ELISA) untuk VEGF-A dan VEGFR-2, serta quantitative reverse transcription-polymerase chain reaction (qRT-PCR) untuk miR-92a. Keluaran klinis sekunder seperti derajat angina, kualitas hidup, 6-minutes walk test (6MWT), dan ejection fraction (EF) juga dinilai.

Hasil: Kadar VEGF-A dan VEGFR-2 dipertahankan pada kelompok ECP, sedangkan kadar VEGF-A dan VEGFR-2 mengalami penurunan yang signifikan pada kelompok sham [VEGF-A ECP vs sham: 1 (-139 to160) vs -136 (-237 to 67) pg/ml, p = 0.026; VEGFR-2 ECP vs sham: -171(-844 to +1166) vs -517(-1549 to +1407) pg/ml, p = 0.021, respectively]. Kadar miR-92a meningkat secara signifikan pada kelompok ECP [5.1 (4.2 – 6.4) to 5.9 (4.8 – 6.4), p<0.001] and sham [5.2 (4.1 – 9.4) to 5.6 (4.8 – 6.3), p=0.008]. Tidak terdapat korelasi antara perubahan kadar VEGF-A, VEGFR-2, dan miR-92a [VEGF-A vs VEGFR-2 (r = 0.243, p = 0.09; uji Spearman), VEGF-A vs miR92-a (r = 0.229, p = 0.11; uji Spearman), dan VEGR-2 vs miR92-a (r = 0.08, p = 0.581; uji Spearman)].

Kesimpulan: ECP mampu mempertahankan angiogenesis dengan cara mempertahankan kadar VEGF-A dan VEGFR-2. Pada kondisi iskemia, baik high shear stress (ECP) maupun low shear stress (sham) dapat menginduksi pelepasan miR-92a. ECP mempengaruhi VEGF-A, VEGFR-2, dan miR-92a secara independen.

.....Background: ECP is able to reduce angina frequency, improve quality of life, and improve exercise time-induced ischemia time. These benefits can last several years after the ECP. The mechanism for the long-term benefit of ECP has been proven by the presence of angiogenesis, which is thought to be mediated by VEGF-A, VEGFR-2, and miR-92a.

Objective: To determine the effect of ECP on VEGF-A and VEGFR-2, and its relationship with miR-92a in patients with refractory angina.

Methods: This study was a double-blind randomized clinical trial involving 50 subjects with refractory angina. Subjects were randomized (1:1) into either ECP or sham therapy groups, each administered for 1 hour, up to 35 times. Plasma VEGF-A, VEGFR-2, and miR-92a levels were measured before and after therapy using the enzyme-linked immunosorbent assay (ELISA) method for VEGF-A and VEGFR-2, as well as quantitative reverse transcription-polymerase chain reaction (qRT-PCR).) for miR-92a. Secondary clinical outcomes such as degree of angina, quality of life, 6-minute walk test (6MWT), and ejection fraction (EF) were also assessed.

Results: VEGF-A and VEGFR-2 levels are maintained in the ECP group, while VEGF-A and VEGFR-2 levels decrease in the sham group [VEGF-A ECP vs sham: 1 (-139 to160) vs -136 (-237 to 67) pg/ml, $p = 0.026$; VEGFR-2 ECP vs sham: -171(-844 to +1166) vs -517(-1549 to +1407) pg/ml, $p = 0.021$, respectively]. MiR-92a levels increase significantly in the ECP group [5.1 (4.2 – 6.4) to 5.9 (4.8 – 6.4), $p<0.001$] and sham [5.2 (4.1 – 9.4) to 5.6 (4.8 – 6.3), $p=0.008$]. There is no correlation between changes in VEGF-A, VEGFR-2, and miR-92a levels [VEGF-A vs VEGFR-2 ($r = 0.243$, $p = 0.09$; Spearman's test), VEGF-A vs miR92-a ($r = 0.229$, $p = 0.11$; Spearman's test), and VEGR-2 vs. miR92-a ($r = 0.08$, $p = 0.581$; Spearman's test)].

Conclusion: ECP therapy is able to maintain angiogenesis by maintaining VEGF-A and VEGFR-2 levels. In ischemic conditions, both high shear stress (ECP) and low shear stress (sham) can induce the release of miR-92a. ECP affects VEGF-A, VEGFR-2, and miR-92a independently.