

# 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 to 160) 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 VEGFR-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 to 160) 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 miR-92a ( $r = 0.229$ ,  $p = 0.11$ ; Spearman's test), and VEGFR-2 vs. miR-92a ( $r = 0.08$ ,  $p = 0.581$ ; 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.