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Role of Angiopoetin 1, Angiopoietin 2 and Endothelial Function in HIV

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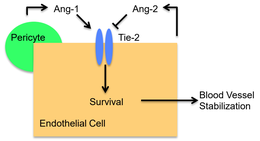
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Background

HIV-infected patients have increased risk for cardiovascular disease (CVD). The underlying mechanism likely involves impaired endothelial dysfunction, a precursor of atherosclerosis. Endothelial dysfunction stems from an imbalance in endothelial homeostasis. This balance is promoted by the Tie2 receptor system through its agonist, angiopoietin-1 (Ang1) while its antagonist, the inflammatory protein angiopoietin-2 (Ang2), promotes endothelial activation. (Figure 1)

Figure 1: Tie-2 Receptor system



Ang1 is constitutively released from pericytes, activating Tie-2, and promoting survival and stability. Ang2 is released from endothelial cells in response to inflammatory stimuli and inhibits Tie-2. Adapted from Imhof and Aurand-Lions, *Nature Medicine,* 12, 171-172 (2006)

Hypothesis

HIV infection results in decreased Ang1 levels and increased Ang2 levels, leading to impaired endothelial function.

Methods

Study design:

- Cross-sectional analysis of 89 HIV-infected individuals, and 46 uninfected controls within the SCOPE cohort from San Francisco General Hospital.

Study Measurements:

- Ang1 and Ang2 levels were measured from serum samples using ELISA assays.
- Endothelial function was measured by flow-mediated vasodilation of the brachial artery (FMD). Measurements include brachial artery diameter at baseline and after 1 minute of reactive hyperemia resulting from 5 minutes of forearm occlusion by a blood pressure cuff. FMD was the percentage of increase from baseline. (Figure 2)

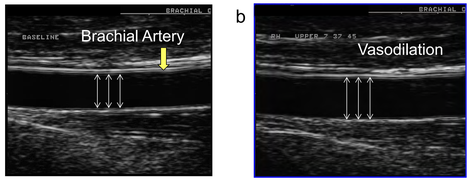
Statistical Analysis:

- Generalized linear regression models and Spearman correlations were used to determine the association of HIV to Ang1 and Ang2 levels and FMD.

Results: Clinical Characteristics

	HIV-uninfected (n = 46)	HIV-infected (n = 89)	p-value
Age, Median years ± SD	53 ± 10	45 ± 12	0.03
Male, N (%)	45 (98)	73 (82)	0.03
Race, N (%)			0.10
African American	19 (41)	20 (23)	
Hispanic	4 (9)	8 (9)	
Non-Hispanic White	20 (44)	57 (64)	
Other	3 (6)	4 (4)	
Comorbidities, N (%)			
Coronary Artery Disease	1 (2)	2 (2)	0.98
Hypertension	13 (28)	29 (33)	0.61
Hyperlipidemia	24 (52)	45 (51)	0.86
Diabetes Mellitus Type 2	1 (2)	5 (6)	0.36
Chronic Kidney Disease (eGFR<60)	1 (2)	12 (13.5)	0.04
Tobacco Dependence	21 (46)	27 (30)	0.08
Medication Use, N(%)			
Aspirin	5 (11)	17 (19)	0.22
Anti-hypertensive	10 (22)	25 (28)	0.42
Statin	6 (13)	15 (17)	0.56
Body Mass Index, Median (IQR)	26 (23 - 28)	25 (23 - 29)	0.54
Framingham Risk Score, Median (IQR)	5 (3 - 9)	3 (1 - 6)	0.01

Figure 2: Brachial Artery Flow Mediated Dilation



Macrovascular function measured by comparison of brachial artery vasodilation before (a) and after (b) restoration of blood flow (reactive hyperemia)

Results: HIV Characteristics

Viral Load, Median (IQR)	40 (40 - 3380)
Duration of HIV infection, Median Years (IQR)	9 (4 - 19)
Treatment Status at Study Visit, N (%)	
Off HAART, VL < 75	4 (5)
Off HAART, VL > 75	35 (39)
On HAART, VL > 75	3 (3)
On HAART, VL < 75	47 (53)
Opportunistic Infection (OI) at visit, N (%)	6 (7)
History of OI, N (%)	46 (52)

Results: Unadjusted Study Measurements

Median (IQR)	HIV-uninfected	HIV-infected	p-value
Angiopoietin 1, pg/ml	**3756 (1567 - 9740)**	**2219 (1022 - 4298)**	**0.01**
Angiopoietin 2, pg/ml	**1839 (1452 - 2350)**	**2147 (1617 - 3106)**	**0.06**
TNF-alpha, pg/ml	3.6 (3.0 - 4.2)	4.3 (3.5 - 5.3)	0.01
C-reactive protein, mg/L	1.4 (0.7 - 3.3)	1.6 (0.8 - 3.4)	0.70
D-dimer, ug/ml	0.2 (0.1 - 0.4)	0.2 (0.1 - 0.5)	0.74
Flow-Mediated Dilation at 60 sec, %	4.4 (2.7 - 5.5)	3.8 (2.6 - 5.6)	0.95

Results: Adjusted Ang1/Ang2 Percent Difference between Groups

	% Difference	p-value
HIV-infected vs HIV-uninfected*		
Angiopoietin 1	**-44**	**0.02**
Angiopoietin 2	9	0.66
HIV-infected on effective suppressive therapy vs HIV-uninfected^		
Angiopoietin 1	**-23**	**0.05**
Angiopoietin 2	-8	0.48

*Adjusted for HIV status, HAART, age, sex, race, CKD
^Adjusted for age, sex, race, HAART, OI, diabetes, tobacco use, CAD

Results: Adjusted Correlation of Ang1/Ang2 to FMD

	% Difference	p-value
Association between Ang1 and FMD	**25**	**<0.001**
Association between Ang2 and FMD	8	0.24

Adjusted for age, sex, race, treatment status

Discussion

- HIV-infected individuals, despite being younger and having lower Framingham Risk Scores, exhibit similar traditional risk factors for cardiovascular disease e.g. hypertension, hyperlipidemia, etc.
- Circulating Ang1 levels are lower among HIV-infected individuals when compared to HIV-uninfected controls.
- When analyzed among HIV-infected individuals on effective suppressive therapy, circulating Ang1 levels remain significantly lower when compared to HIV-uninfected individuals suggesting a correlation between HIV infection and imbalances in angiopoietin levels.
- In this cohort, Ang2 levels are not significantly different between HIV-infected and uninfected groups after adjustment for traditional risk factors.
- Lower Ang1 levels are independently associated with worsened flow-mediated dilation.
- Ang2 levels are not independently associated with increased endothelial dysfunction.

Conclusions

HIV infection leads to an imbalance between Ang1 and Ang2. This imbalance within the Tie-2 receptor system leads to a disturbance of endothelial homeostasis. Our findings reveal a potential new target for mitigating CVD risk in the setting of treated HIV infection.

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