The role of HIF-1α, VEGF and Obstructive Sleep Apnoea in the Development of Coronary Collateral Circulation

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Introduction

Intermittent hypoxia (IH) in obstructive sleep apnoea (OSA) confers cardio-protection by enhancing coronary collateral circulation (CCC) development, decreasing myocardium vulnerability to hypoxia and ischaemia. The human CCC is able to keep up with myocardial demand during episodes of acute coronary occlusion in up to 33% of patients making it a useful marker for predicting myocardial vulnerability.[1]

IH during sleep promotes the generation of reactive oxygen species (ROS) and stimulates the transcription of HIF-1α, a pro-angiogenic growth factor that regulates the transcription of vascular endothelial growth factor (VEGF).[2] This brings about changes in collateral vasomotor and viscoelastic properties in order to ensure an adequate collateral flow index (CFI).[3] CCC would then be able to salvage hypoperfused or hypoxic myocardium, possibly even avoiding transmural MI and death all-together.[4] Berger et al. (2013) have also shown that VEGF expression in OSA patients presenting with acute MI is higher when compared to non-OSA patients. Endothelial progenitor cells were also said to mobilise more in the OSA group. Both these findings suggest that neovascularisation and a better angiogenic capacity may be a means of conferring cardioprotection in OSA patients presenting with ischemia.[5] Studies looking specifically at patients with OSA also seem to suggest a survival advantage in elderly patients, implying better protection thanks to more extensive ischaemic pre-conditioning with age.[6]

Objective

The main objective was to assess whether hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) play a role in the development of CCC in patients with OSA.

Methodology

- Sample Population
  - Cases: 44 patients with reported collaterals on angiography
  - Controls: 21 patients not having a CCC
- Testing
  - All patients underwent ambulatory polysomnography
  - Epworth Sleepiness Scale Questionnaire
  - Blood samples for HIF-1α and VEGF levels were taken
  - CCC reviewed by 2 independent cardiologists
    - Separate interpretation done by a third cardiologist if Rentrop Score fails to match

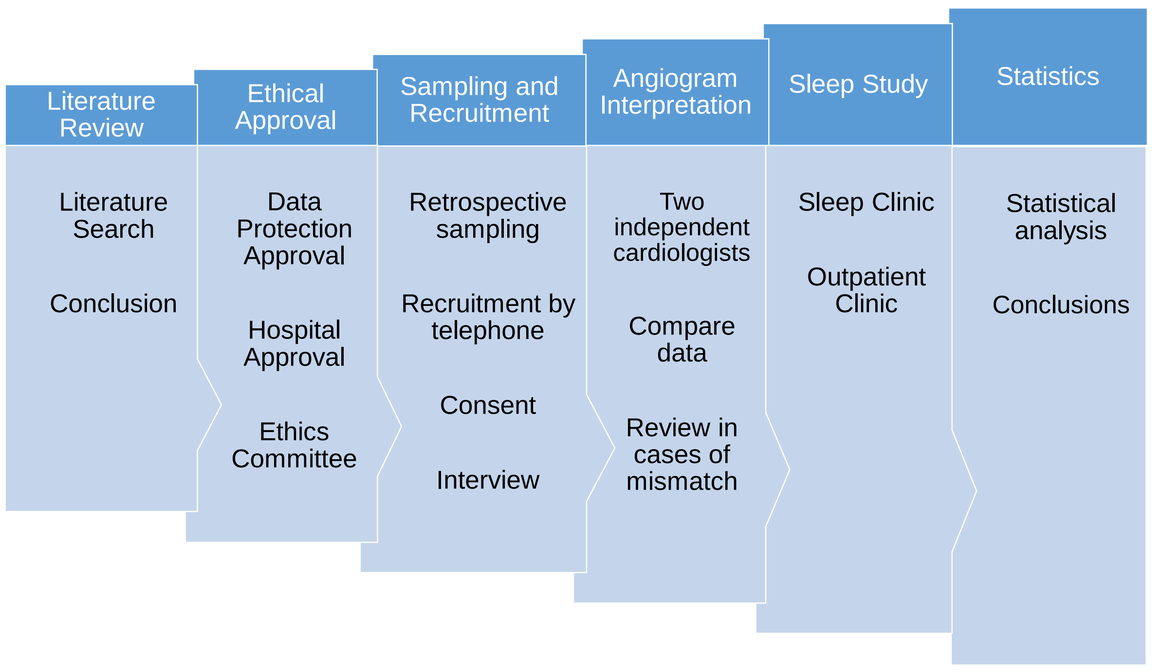

Figure 1: Methodology

Baseline Characteristics

Variables	Sample (n=65)	Cases (n=44)	Controls (n=21)	P-value
Mean Age	64.8 ± 9.1	65.5 ± 10.3	63.1 ± 5.9	0.23
Age Group, n (%)				
40-49		3 (6.7)	0 (0.0)	0.08
50-59		9 (22.2)	4 (19.0)	
60-69		19 (42.2)	16 (76.2)	
70-79		10 (22.2)	1 (4.8)	
80-89		3 (6.7)	0 (0.0)	
Gender, n (%)				
Male	52 (80.0)	38 (86.7)	14 (66.7)	0.06
Female	13 (20.0)	6 (13.3)	7 (33.3)	
Smoking status				
Non-smokers	21 (32.3)	11 (25.0)	10 (47.6)	0.19
Ex-smokers	36 (55.4)	26 (59.1)	9 (42.9)	
Active smokers	8 (12.3)	7 (15.9)	2 (9.5)	
Height, cm	165.1 ± 9.8	166.8 ± 8.9	161.0 ± 10.9	0.03
Weight, kg	81.8 ± 16.0	84.8 ± 15.8	75.2 ± 14.1	0.02
Body Mass Index, kg/m²	30.0 ± 4.8	30.5 ± 5.1	28.9 ± 4.0	0.20
Neck Circumference, cm	41.7 ± 4.7	42.6 ± 4.8	39.8 ± 4.3	0.02
Epworth Sleepiness Scale	6.7 ± 3.9	6.5 ± 3.7	7.3 ± 3.9	0.39
Hypertension, n (%)	38 (58.5)	25 (56.8)	13 (61.9)	0.70
Diabetes Mellitus, n (%)	28 (43.1)	20 (44.5)	8 (38.1)	0.58
Acute Coronary syndrome, n (%)	41 (64.1)	29 (65.9)	12 (57.1)	0.31
Percutaneous coronary intervention, n (%)	44 (67.7)	28 (65.1)	16 (76.2)	0.37
Coronary artery bypass graft, n (%)	25 (38.5)	17 (38.6)	8 (38.1)	0.97
Cerebrovascular Accident, n (%)	2 (3.1)	2 (4.5)	0 (0.0)	0.32
Peripheral Vascular Disease, n (%)	3 (4.6)	3 (6.8)	0 (0.0)	0.22
Chronic Heart Failure, n (%)	15 (23.1)	14 (31.8)	1 (4.8)	0.02
Cardiac devices, n (%)	5 (7.7)	5 (11.4)	0 (0.0)	0.11
New York Heart Association Class, n (%)				
Class 0	41 (63.1)	24 (54.5)	17 (81.0)	0.19
Class 1	15 (23.1)	11 (25.0)	4 (19.0)	
Class 2	6 (9.2)	6 (13.6)	0 (0.0)	
Class 3	2 (3.1)	2 (4.5)	0 (0.0)	
Class 4	1 (1.5)	1 (2.q)	0 (0.0)	
Angina, n (%)	6 (9.2)	1 (2.3)	5 (23.8)	0.01

Results

- There was no difference in patients suffering from OSA (irrespective of severity) in cases and controls

Sleep study result	Cohort (n=65)	Cases versus Controls		
		Cases (n=44)	Controls (n=21)	P-value
Sleep study outcome				
Sleep apnoea present (%)	50 (76.9)	35 **(79.5)**	15 **(71.4)**	0.47
Sleep apnoea absent (%)	15 (23.1)	9 (20.5)	6 (28.6)	
Sleep study result				
Normal/Mild sleep apnoea (%)	37 (56.9)	23 (52.3)	14 (66.7)	0.27
Moderate/Severe sleep apnoea (%)	28 (43.1)	21 (47.7)	7 (33.3)	

- Rentrop Score did not change significantly with OSA severity

Obstructive Sleep Apnoea	Mean Rentrop score ± SD	95% Confidence Interval for Mean Rentrop score		P-value
		Lower	Upper	
Absent	1.94 ± 1.00	1.41	2.47	0.51
Mild	2.38 ± 1.16	1.85	2.91	
Moderate	2.40 ± 1.18	1.74	3.06	
Severe	2.46 ± 0.88	1.93	2.99	

- Moderate/Severe OSA patients had significantly higher HIF-1α with higher Rentrop Scores, with no significant difference with VEGF.

OSA Status	Variable (pg/mL)	Rentrop 0	Rentrop 1	Rentrop 2	Rentrop 3	P-value
Absent or Mild	HIF-1α	400.07 ± 226.59	287.76 ± 226.59	501.41 ± 465.72	739.22 ± 356.70	0.49
	VEGF	0.90 ± 1.59	22.60 ± 52.54	3.09 ± 7.27	0.00 ± 0.00	0.23
Moderate or Severe	HIF-1α	171.80 ± 177.21	876.41 ± 603.52	766.58 ± 646.30	1181.09 ± 357.06	0.02
	VEGF	0.15 ± 0.39	4.32 ± 10.43	2.33 ± 7.26	12.62 ± 21.79	0.29

- No significant difference between diabetic and non-diabetic patients for HIF-1α (p=1.00 [absent/mild]; p=0.83 [moderate/severe] and VEGF (p=0.34 [absent/mild]; p=0.45 [moderate/severe])

Conclusions

- OSA was common in both cases (79.5%) and controls (71.4%) highlighting it's elevated prevalence in such a cohort
- HIF-1α is significantly higher in moderate and severe OSA patients implying that these patients are more able to augment their collateral circulation

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