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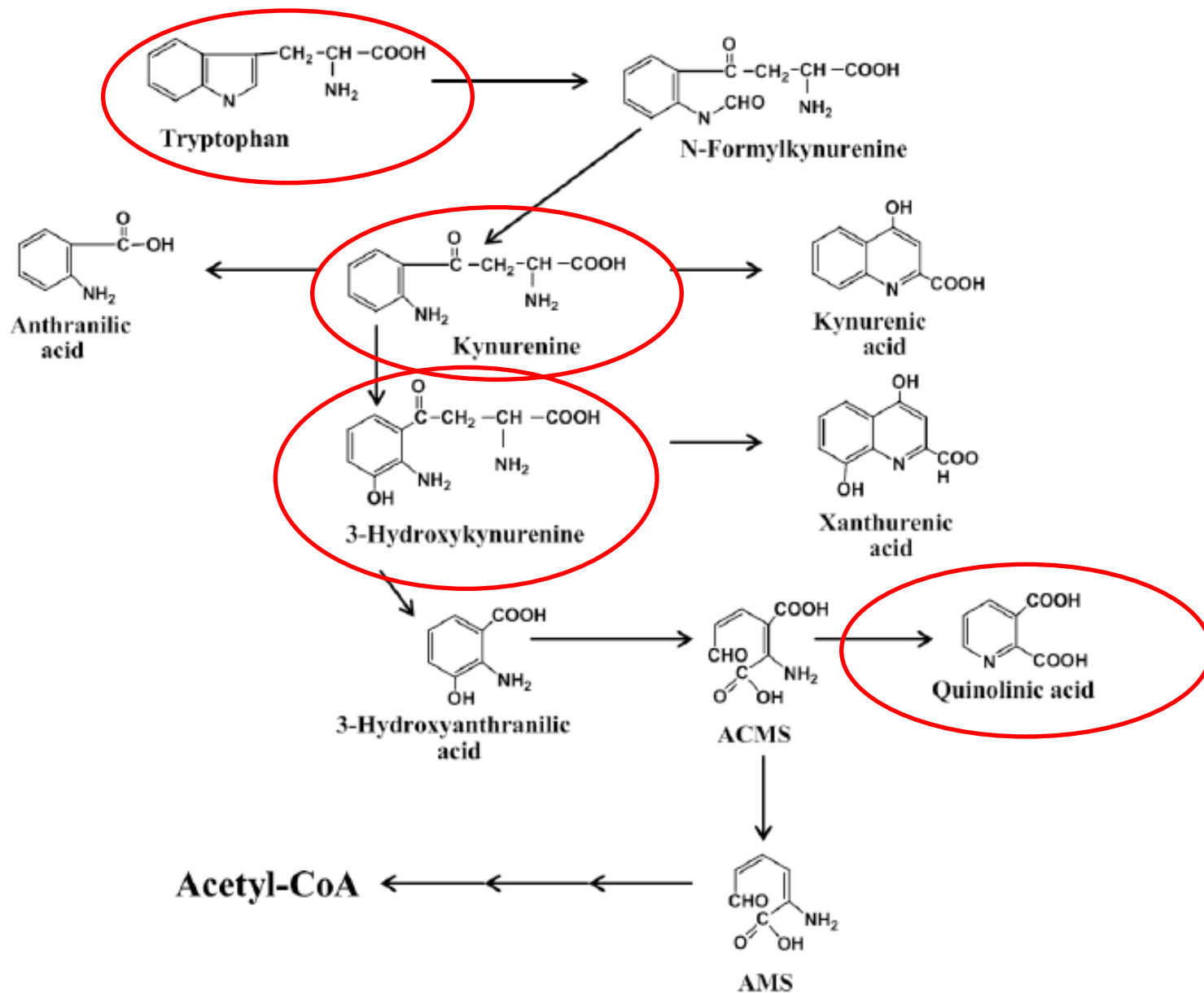
Tryptophan, Kynurenine and Quinolinic Acid

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What are they good for?

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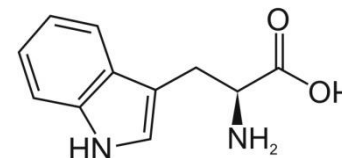


Tryptophan-kynurenine pathway: Acceleration upon Inflammation

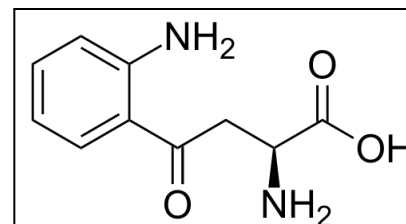
IFN- γ , IFN- β , IFN- α , TNF- α ...

Indolamin-2,3-
dioxygenase (IDO)

Tryptophan



Kynurenine

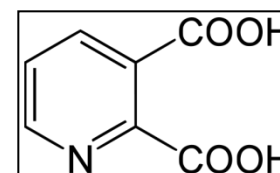


Kynureninase

3-hydroxy-anthranilate

3,4-dioxygenase

Quinolinic acid



„Neurotoxin, gliotoxin, proinflammatory
mediator, prooxidant molecule“

Activation of NAD(P)H Oxidase by tryptophan-derived 3-hydroxykynurenine Accelerates Endothelial Apoptosis and Dysfunction *In Vivo*

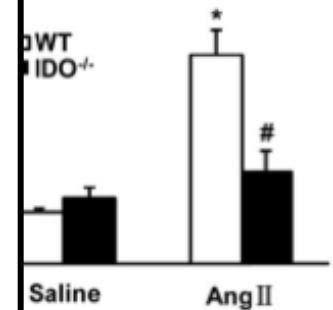
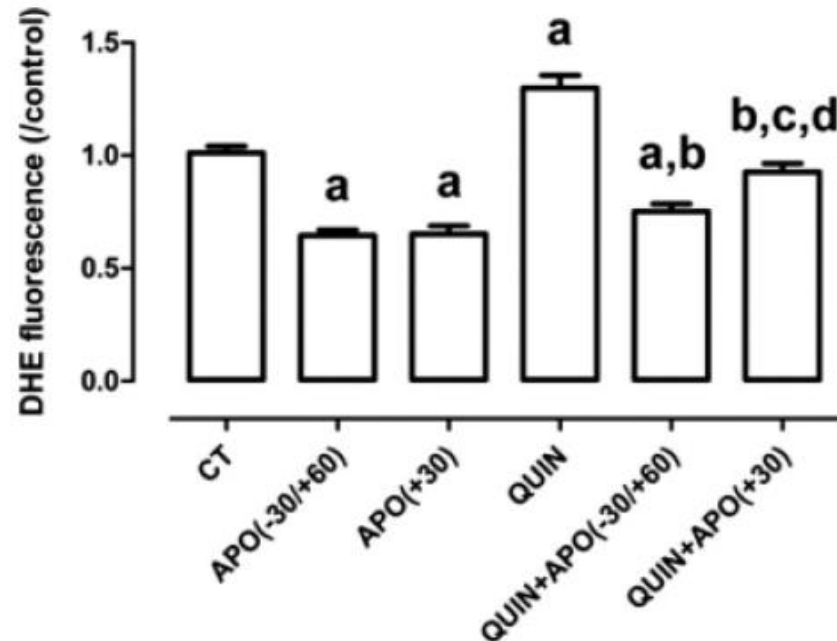
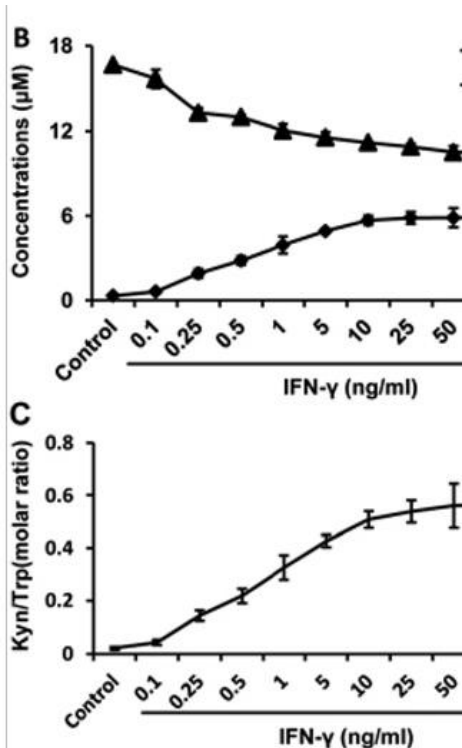


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Qiongxin Wang, Miao Zhang, Ye Ding, Qilong Wang, Wenheng Zhang, Bing Song, and Ming-Hui Zou

Section of Molecular Medicine, Department of Molecular Biology, University of Oklahoma, USA

Quinolinic acid induces superoxide anion production in rat striatal cells



Maldonado et al. *Journal of Neuroscience Research* 88:620–629 (2010)

Wang et al. *Circ Res* 2014 January 31; 114(3): 480–492.

Development of a liquid chromatography–mass spectrometry method for the determination of the neurotoxic quinolinic acid in human serum

Andreas Meinitzer ^{a,*}, Andreas Tomaschitz ^{b,c}, Stefan Pilz ^d, Manfred Truber ^a, Gabriele Zechner ^a, Martin Gaksch ^d, Barbara Prietl ^d, Gerlies Treiber ^d, Michaela Schwarz ^e, Andreas Baranyi ^f

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Characteristics of the quinolinic acid method.

	Quinolinic acid	
Working range [nmol/L]	50–5000	
Calibration curve		
Slope	0.03725	
Intercept	0.00224	
Correlation r^2	0.9998	
Intra-day precision $n = 6$	Low	High
Mean [nmol/L]	225	725
SD [nmol/L]	10.2	8.5
Coefficient of variation [%]	4.5	1.2
Inter-day precision $n = 20$		
Mean [nmol/L]	229	752
SD [nmol/L]	17.0	47.3
Inter-day variability [%]	7.2	6.3
Recovery (mean extraction efficiency) [% $\pm$ SD]	95.0 $\pm$ 7.7	
Limit of quantification (LOQ) [nmol/L]	50	
SD [nmol/L]	4.7	
Coefficient of variation [%]	9.3	
Limit of detection (LOD) [nmol/L]	15	
3-fold SD of the baseline noise		
Stability in the matrix tested	2 days	

Patients characteristics and quinolinic acid concentration.

Number of patients	50
Females [%]	64
Age [yrs]	31 $\pm$ 8
Body mass index [kg/m ²]	23.3 $\pm$ 4.3
Systolic blood pressure [mm Hg]	129 $\pm$ 15
Diastolic blood pressure [mm Hg]	84 $\pm$ 10
Glucose [mmol/L]	4.89 $\pm$ 0.92
HDL-cholesterol [mmol/L]	1.84 $\pm$ 0.37
LDL-cholesterol [mmol/L]	2.46 $\pm$ 0.57
Triglycerides [mmol/L]	1.08 $\pm$ 0.49
Quinolinic acid [nmol/L]	350 $\pm$ 167

Continuous variables are presented as means $\pm$ standard deviation (SD).

STUDY PROTOCOL

Open Access

Effect of eplerenone on parathyroid hormone levels in patients with primary hyperparathyroidism: a randomized, double-blind, placebo-controlled trial

Andreas Tomaschitz^{1*†}, Astrid Fahrleitner-Pammer², Burkert Pieske¹, Nicolas Verheyen¹, Karin Amrein², Eberhard Ritz³, Katharina Kienreich², Jörg H Horina⁴, Albrecht Schmidt¹, Elisabeth Kraigher-Krainer¹, Caterina Colantonio¹, Andreas Meinitzer⁵ and Stefan Pilz^{2,6*†}

In/Exclusion criteria:

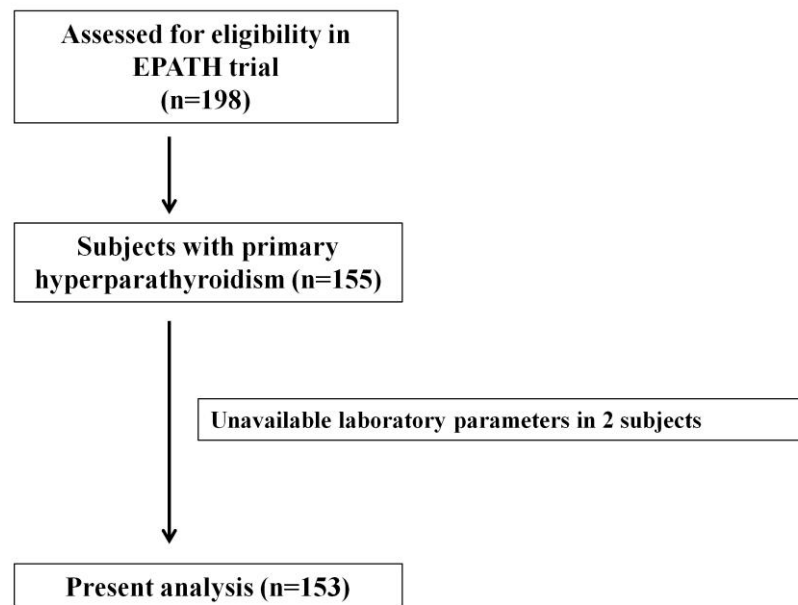
- **Primary hyperparathyroidism (biochemical diagnosis)**
- **Age > 18**
- **no acute illness**

Blood sampling and storage at -80 °C

- **Tryptophan**
- **Kynurenine**
- **Quinolinic acid**

24-hour ambulatory blood pressure monitoring

Echocardiography



Effect of eplerenone on parathyroid hormone levels in patients with primary hyperparathyroidism: a randomized, double-blind, placebo-controlled trial



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Baseline characteristics

Age, years	67 +/- 10
Females, n (%)	104 (78%)
Body mass index, kg/m ²	27 +/- 5
Smokers, n (%)	50 (38%)
Estimated glomerular filtration rate (CKDEPI), mL/min/1.73m ²	77 +/- 16
Total cholesterol, mg/dL	202 +/- 43
HbA1c, mmol/mol	37 (35 – 40)
GFR, ml/min/m ²	78 +/- 16
Total cholesterol, mg/dL	202 +/- 43

Tryptophan-kynurenine pathway

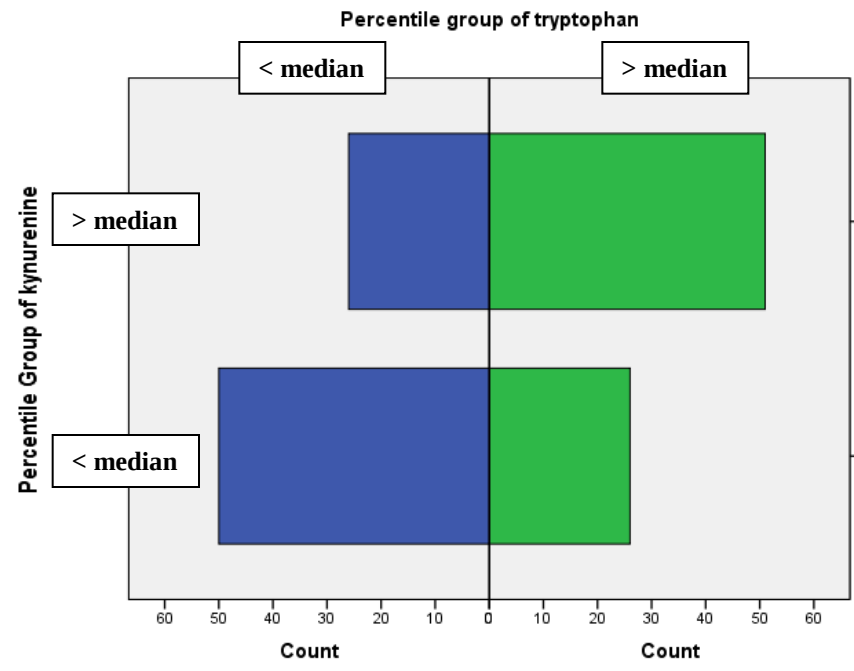
Tryptophan, µmol/L	55.9 +/- 10.0
Kynurenine, µmol/L	2.8 +/- 0.8
Quinolinic acid, nmol/L	497 (406 – 633)

Cardiovascular parameters

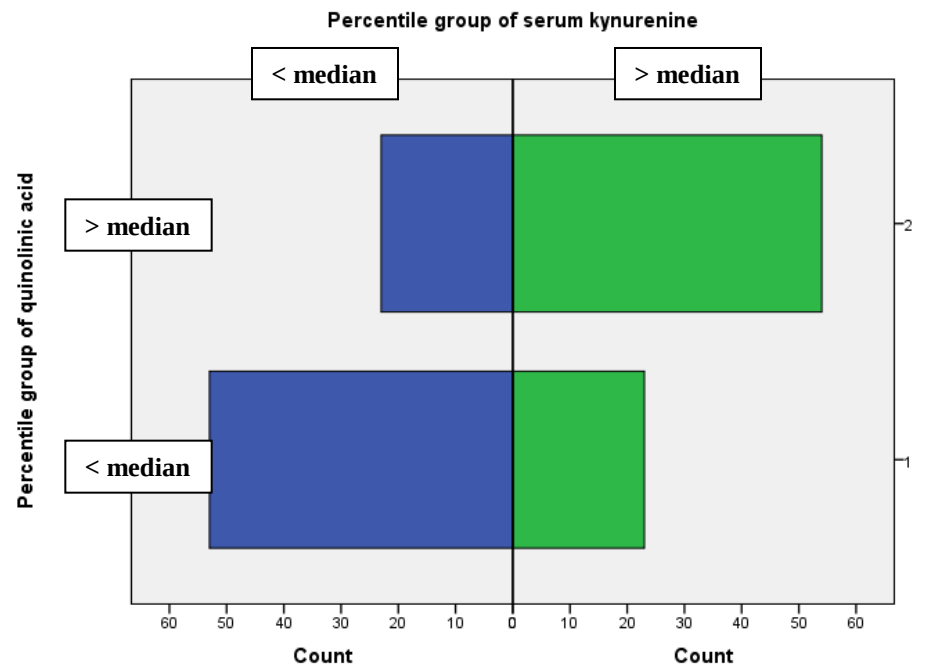
Left ventricular ejection fraction, %	63 (59 – 68)
E/e' (average)	10.1 (8.1 – 12.9)
e', m/s (average)	7.1 +/- 2.3
Left ventricular mass index, g/m ²	102 (81 – 123)
Left ventricular hypertrophy, n (%)	70 (45 %)
Left atrial volume index, ml/m ²	30 (23 – 36)
Left atrial dilatation, n (%)	83 (54%)
Mean 24h systolic BP, mmHg	122 +/- 11
Mean 24h diastolic BP, mmHg	73 +/- 7
Mean nighttime systolic BP, mmHg	113 +/- 14
Mean nighttime diastolic BP, mmHg	65 +/- 9
Arterial hypertension, n (%)	97 (73%)
Antihypertensive medication , n (%)	85 (64%)

Effect of eplerenone on parathyroid hormone levels in patients with primary hyperparathyroidism: a randomized, double-blind, placebo-controlled trial

High tryptophan → high kynurenine?



High kynurenine → high quinolinic acid?



Effect of eplerenone on parathyroid hormone levels in patients with primary hyperparathyroidism: a randomized, double-blind, placebo-controlled trial



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Determinants of tryptophan, kynurenine and quinolinic acid in multivariate linear regression analyses

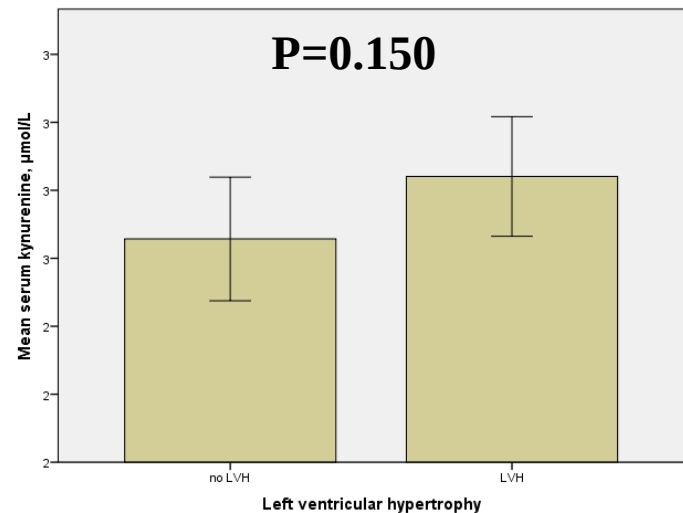
	Tryptophan		Kynurenine		Quinolinic acid	
	β	P	β	P	β	P
Age	ns		ns		0.180	0.003
Gender	0.304	<0.001	0.131	0.045	ns	
BMI	0.187	0.040	ns		ns	
eGFR (CKDEPI)	ns		-0.525	<0.001	-0.275	<0.001
Total cholesterol	0.147	0.072	-0.163	0.012	ns	
Diabetes mellitus	ns		ns		ns	
C-reactive protein	ns		0.167	0.017	0.154	0.007
Tryptophan	-		0.452	<0.001	-0.051	0.403
Kynurenine	-		-		0.554	<0.001

Left ventricular hypertrophy

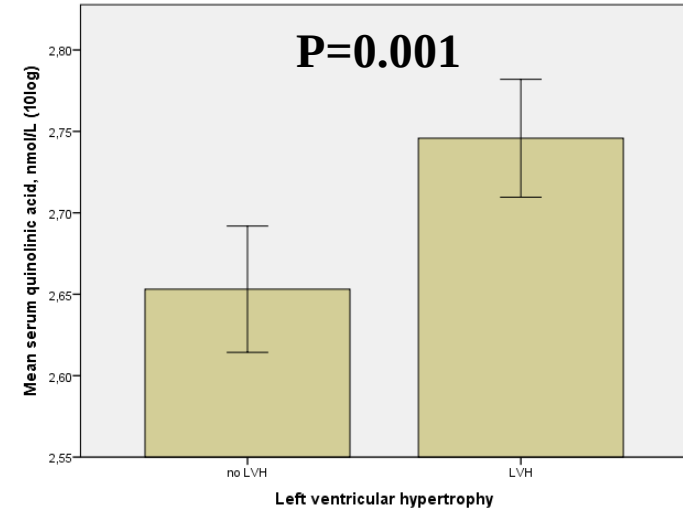


Kynurenine

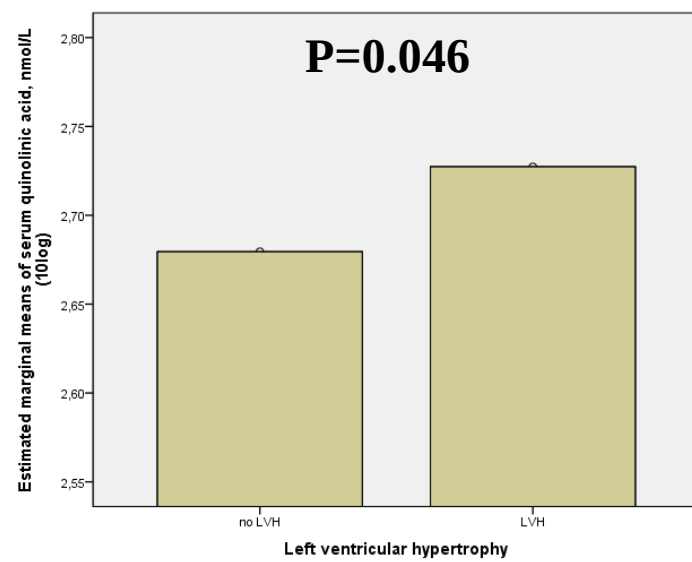
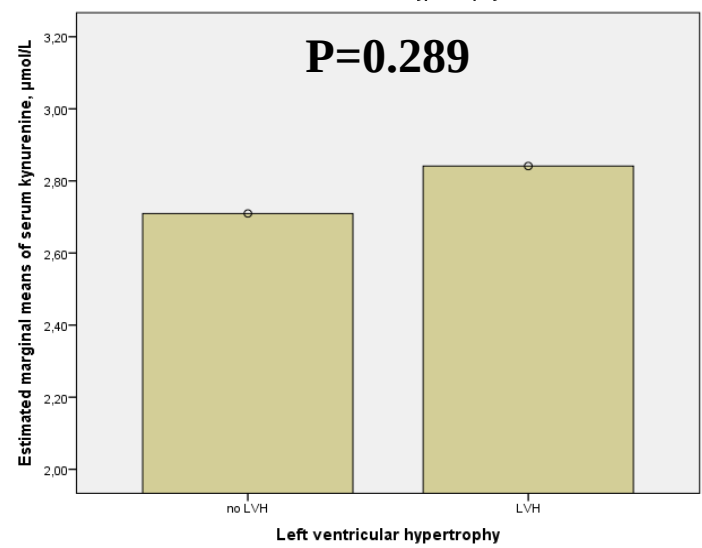
T-test



Quinolinic acid



Analysis of Covariance

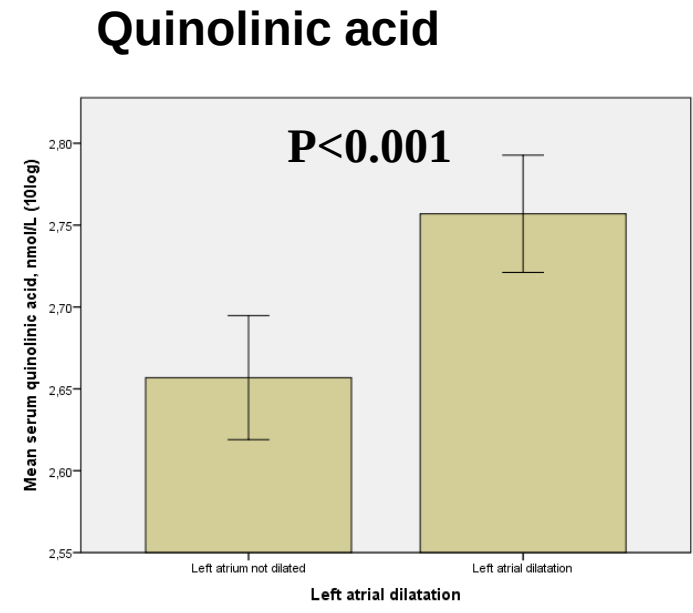
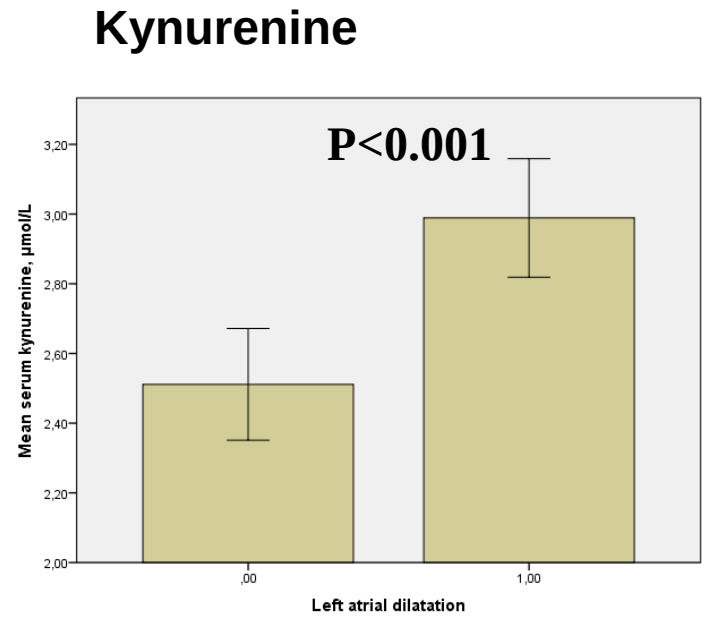


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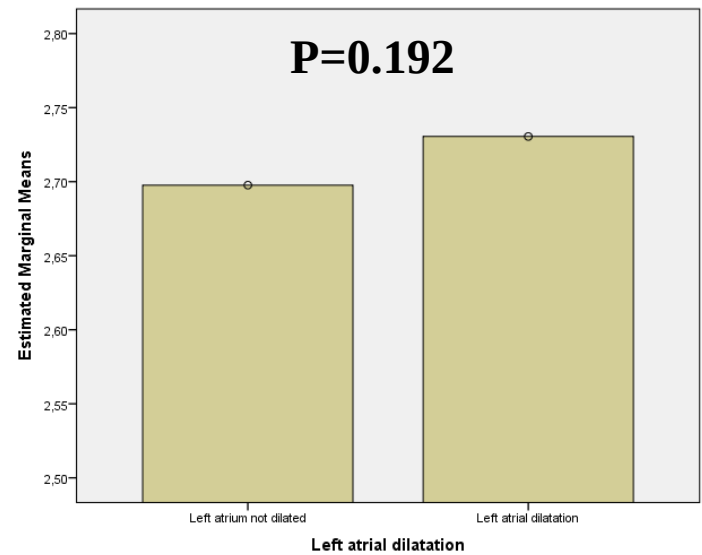
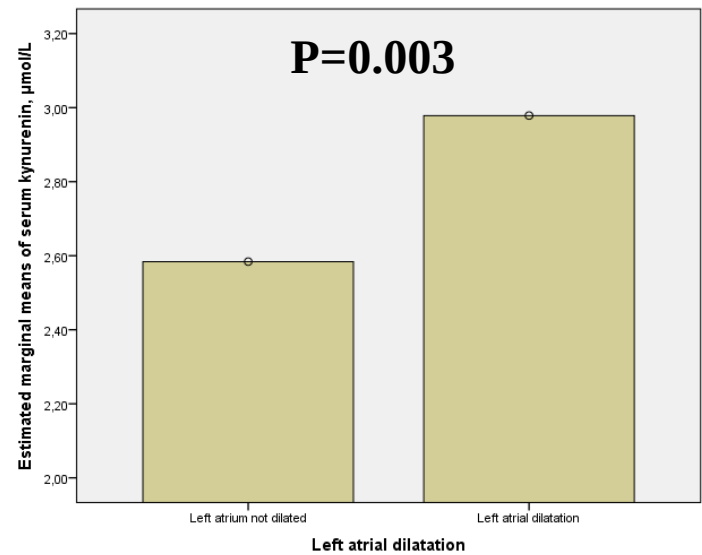
Left atrial dilatation



T-test



Analysis of Covariance



Conclusions



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- **Quinolinic acid levels are not independently related with tryptophan levels**
- **Independent correlation with cardiac structure and function**
- **Cause-effect relationship unclear**
 - **direct effects?**
 - **epiphenomenon 3-OH kynurenine?**
- **Mechanisms to be elucidated**

Acknowledgments

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