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Vesa Oikonen

Analysis of renal perfusion from [^{15}O]H_2O PET studies

Literature review

In all published studies, the standard one-tissue compartment model with parameters RBF (renal blood flow), p (partition coefficient, and RBV (renal blood volume) was used.

Table 1. Published studies applying [^{15}O]H_2O PET for estimating cortical renal blood flow.

Study	Fitted parameters	Constraints	Model input	Delay correction	Dispersion correction	Recovery correction	Scan length	Results
Inaba 1989	RBF, p	RBV from [^{15}O]CO scan	?	?	?	?	?	RBF = 1.7 ± 0.6 (0.9-2.9) ml/min/g
Nitzsche 1993	RBF, p, RBV	-	arterial blood, 10 s intervals	Adjusted by Peak times of aortic and arterial TACs	-	yes	300 s	RBF = 4.70 ± 0.28 ml/min/g RBV = 0.16 ± 0.11 ml/g
Middlekauff 1995, 1997, 2000, 2001	RBF, p, RBV	-	abdominal aorta (by Germano 1992)	Probably not	-	yes	300 s, of which 120 s used	Controls: about 4 ml/min/g; Heart failure patients: about 2-3 ml/min/g
Juillard 2000, 2002	RBF, delay, RBV	p=1	Abdominal aorta using 80% threshold	fitted as one parameter	-	no	200 and 240 s	Pigs: RBF = 2.5 ± 0.7 ml/min/g RBV = 9 ± 7% Delay = 4 ± 2 s; Humans with chronic renal failure: RBF = 2.2 ± 0.2 ml/min/g
Alpert 2002	RBF, RBF/p Parametric maps using linearized model	RBV=0 ?	Abdominal aorta, corrected using measured diameter	no	no	no	90 s (3 s frames)	Controls: RBF = 3.2 ± 0.4 (2.8-3.8); Renal dysfunction: 2.1 ± 1.1 (1.0-4.1) ml/min/ml
Anderson 2003a, 2003b	RBF, p	RBV from [^{15}O]CO scan	arterial blood with pump	Manually adjusted for individual patients	Measured dispersion in tubing was corrected. Additional manual correction.	no	360 s	RBF = 0.77-2.88 ml/min/ml p = 0.52 – 0.78 ml/ml RBV = 0.11-0.29 ml/ml

Different parameters were selected to be fitted or constrained by different groups. The most surprising selection was made the group which decided to set partition coefficient to 1.0, while the measured values of p are usually well below it. In my experience, this would lead to a very poor fit between the model and data. RBV was included in all studies as one of the fitted parameters or as measured with [^{15}O]CO scan, except by Alpert et al. 2002.

In most studies, the input curve was retrieved from the aortic ROI in the PET image. In these studies the input curve was usually not corrected for time delay. Dispersion of the input curve was corrected only by one group; these were also the only studies where on-line sampler was used to collect the arterial blood curve. It seems that dispersion correction is not necessary with manual blood sampling or when retrieving input function from the aortic region in PET image.

Relatively poor spatial resolution of PET and partial volume effects will result in underestimation of cortical radioactivity concentration and RBF. In the studies where these effects were corrected for, the RBF estimates were considerably higher than in other studies. Alpert et al. 2002 achieved relatively high RBF estimates without applying any recovery correction, but this may be caused by overestimation of RBF because RBV was not accounted for in their model.

Developing detailed analysis method for Turku PET Centre

Time delay correction

For analysis of regional average TACs there are two options: fit the time delay as an extra parameter in the model, or fit and correct the time delay to the input curve before the model fit. For analysis of dynamic PET image only the latter option is available. Therefore it is necessary to test that both methods produce comparable results.

In the case of renal perfusion studies, the count rate curves, or average curve extracted from the whole PET image, may not be adequate for the delay time fitting, because there are regions inside the imaging field where the radioactivity appears noticeably earlier than in the renal cortex. Therefore, time delay probably must be determined based on input curve and renal curves only.

These alternatives are studied as reported in Appendix A. In conclusion: Time delay can be estimated before perfusion model fit. Countrate curve must no be used in time delay fitting.

Dispersion correction

Dispersion constant of arterial TAC in the measurement system tubing has been measured, and will be applied to all studies with arterial blood input. However, the physiological dispersion constant is not known. It is unlikely that it could be reliably estimated as one fitted parameter, because other variables (RBV, time delay, RBF) are all dependent on each others. What can be done is to apply different values of physiological dispersion constant and observe how large effect it has on the RBF estimates. If a certain dispersion constant would provide a clearly better fit between the model and data, that constant could be considered to be used in all studies, in somewhat similar fashion as in the studies of Anderson et al. (2003a, 2003b).

The effect of dispersion correction is studied in Appendix B. In conclusion: Based on the measured blood and PET data it is not possible to recommend a single dispersion constant that could be applied to all studies. However, if dispersion constant has a value that has been traditionally used, using it should be continued to preserve the level of blood flow estimates. Omitting dispersion correction may lead to considerable underestimation of RBF (up to 50%) and overestimation of RBV.

Recovery correction

Because the final aim is to produce parametric images, no recovery or partial volume correction method will be applied.

RBV

The linearized one-tissue model that was used by Alpert et al. (2002) to produce parametric images, did not contain RBV as a third parameter, although it in theory can easily be incorporated also in the linearized model. It is probable that including RBV as third parameter will lead to higher variability of RBF and noisier RBF images, but omitting it will lead to positive bias in RBF estimates and artefacts in RBF images. Visual comparison of RBF images produced without or with fitted RBV will determine which method will be selected for use in clinical analyses.

Inclusion of RBV as the third parameter in calculation of parametric images was investigated in Appendix C. In conclusion: Multilinear method with RBV as the third parameter produce RBF and RBV images of acceptable quality and similar regional values than analysis from regional average TACs using traditional non-linear one-compartment model.

Recommended analysis method for Turku PET Centre

Processing of input data

Before processing input data, renal ROIs (do not need to be accurate) must be defined and average TACs calculated and saved absolutely without any aortic or other than renal regions. Correct the blood data for dispersion using the same dispersion constants as in other studies with arterial line and the same blood collection system. Estimate the time delay against the renal TACs defined before.

Analysis using regional average TACs

Apply one-tissue compartment model with parameters RBF, p and RBV.

Pixel-by-pixel analysis to produce RBF images

Apply one-tissue compartment model with parameters RBF, p and RBV.

References

Alpert NM, Rabito CA, Correia DJA, Babich JW, Littman BH, Tompkins RG, Rubin NT, Rubin RH, Fischman AJ. Mapping of local renal blood flow with PET and $H_2{}^{15}O$. J. Nucl. Med. 2002; 43: 470-475.

Anderson HL, Yap JT, Miller MP, Robbins A, Jones T, Price PM. Assessment of pharmacodynamic vascular response in a phase I trial of combretastatin A4 phosphate. J. Clin. Oncol. 2003a; 21: 2823-2830.

Anderson H, Yap JT, Wells P, Miller MP, Propper D, Price D, Harris AL. Measurement of renal tumour and normal tissue perfusion using positron emission tomography in a phase II clinical trial of razoxane. Br. J. Cancer 2003b; 89: 262-267.

Germano G, Chen BC, Huang S-C, Gambhir SS, Hoffman EJ, Phelps ME. Use of the abdominal aorta for arterial input function determination in the hepatic and renal PET studies. J. Nucl. Med. 1992; 33: 613-620.

Inaba T, Yamashita M, Kawase Y, Nakahashi H, Watanabe H. Quantitative measurement of renal plasma flow by positron emission tomography with oxygen-15 water. Tohoku J. Exp. Med. 1989; 159: 283-289.

Juillard L, Janier MF, Fouque D, Cinotti L, Maakel N, Le Bars D, Barthez PY, Pozet N, Laville M. Dynamic renal blood flow measurement by positron emission tomography in patients with CRF. Am. J. Kidney Dis. 2002; 40: 947-954.

Juillard L, Janier MF, Foucue D, Lionnet M, Le Bars D, Cinotti L, Barthez P, Gharib C, Laville M. Renal blood flow measurement by positron emission tomography using ^{15}O-albeled water. Kidney Int. 2000; 57: 2511-2518.

Middlekauff HR, Nitzsche EU, Hamilton MA, Schelbert HR, Fonarow GC, Moriguchi JD, Hage A, Saleh S, Gibbs GG. Evidence for preserved cardiopulmonary baroflex control of renal cortical blood flow in humans with advanced heart failure. Circulation 1995; 92: 395-401.

Middlekauff HR, Nitzsche EU, Hoh CK, Hamilton MA, Fonarow GC, Hage A, Moriguchi JD. Exaggerated renal vasoconstriction during exercise in heart failure patients. Circulation 2000; 101: 784-789.

Middlekauff HR, Nitzsche EU, Hoh CK, Hamilton MA, Fonarow GC, Hage A, Moriguchi JD. Exaggerated muscle mechanoreflex control of reflex renal vasoconstriction in heart failure. J. Appl. Physiol. 2001; 90: 1714-1719.

Middlekauff HR, Nitzsche EU, Nguyen AH, Hoh CK, Gibbs GG. Modulation of renal cortical blood flow during static exercise in humans. Circ. Res. 1997; 80: 62-68.

Nitzsche EU, Choi Y, Killion D, Hoh CK, Hawkins RA, Rosenthal JT, Buxton DB, Huang SC, Phelps ME, Schelbert HR. Quantification and parametric imaging of renal cortical blood flow in vivo based on Patlak graphical analysis. Kidney Int. 1993; 44: 985-996.