Is primary CMV infection post-transplant influenced by circadian rhythms?

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Background

- CMV important in transplant patients, due to primary infection, reactivation or reinfection
- Immunosuppression post-transplant increases risk of CMV infection
  - CMV DNA monitored for 100 days in blood
  - Patients in 4 groups depending on donor/ recipient status: D+R-, D+R+, D-R+, D-R-
  - In our centre we use pre-emptive treatment –treated after >3000 copies/ml until 2 negative results, except for D+R- group treated for any positive result for at least 21 days
- Circadian rhythms are diurnal cycles controlling the body at many different organizational levels (see figure 1)
- There has recently been some evidence that viruses and the immune system are affected by circadian rhythms[1-4]

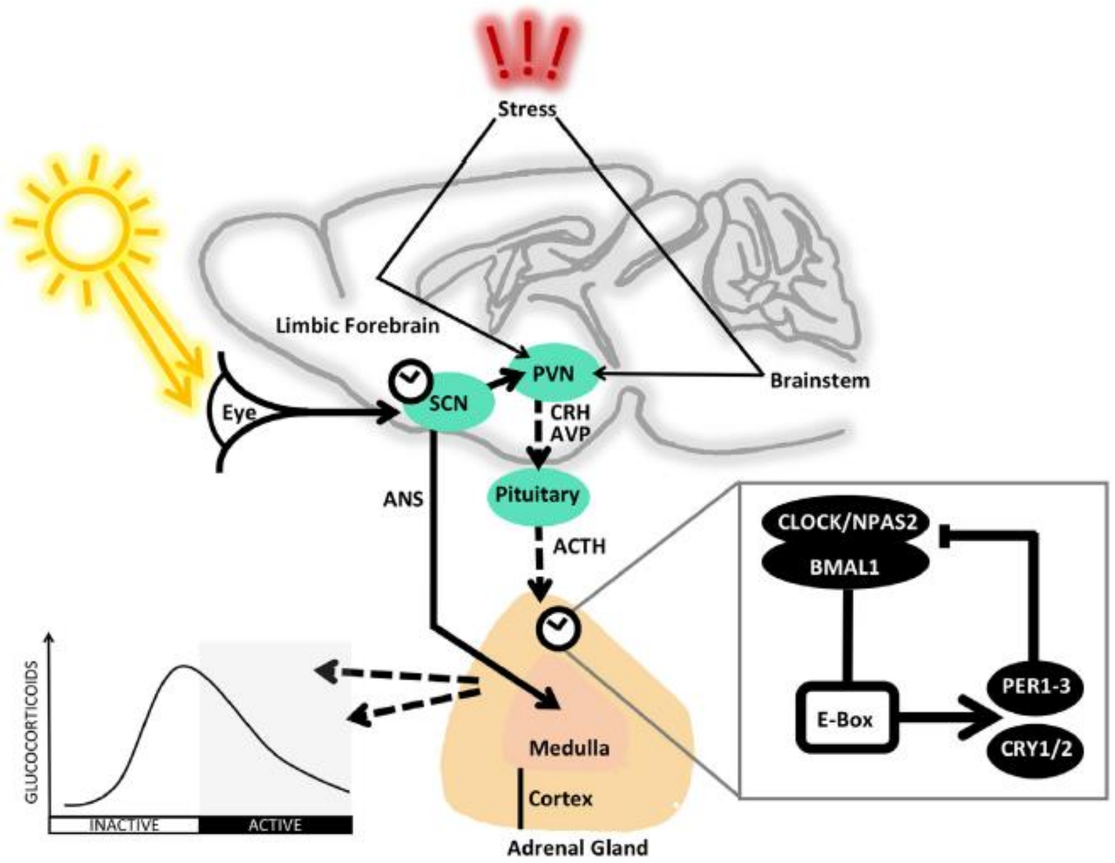


Figure 1 – illustrating different levels of circadian rhythm in the body, From Dumbell et al 2016 Frontiers in Endocrinology[5]

Hypotheses

- Circadian rhythms influence CMV viraemia post-transplant
- Effects will vary based on donor/recipient serostatus
  - D+R- CMV viraemia will vary with time of circulatory arrest of donor
  - D-R+ CMV viraemia will vary with time of organ reperfusion in recipient
  - D+R+ a combination of the above?

Methods

- Data collected from database of all renal and liver transplant patients at Royal Free Hospital London 2002-2015
- Excluding patients transplanted >1 time during study period, multiple organ transplants, transplant not at Royal Free
- Data collected retrospectively:
  - Demographic data
  - Viraemia parameters
  - Transplant timings (see figure 2)
- Timings were divided into 4 categories: “Morning”, “Day", "Evening”, “Night” based on advice from DW (circadian rhythm professor)

References

1. Labreque and Cermakian, J Biol Rhythms. 2015; 30(4):277-90
2. Long et al, Vaccine. 2016; 34(24):2679-85
3. Edgar et al Proc Natl Acad Sci USA. 2016; 113(36):10085-90
4. Collaco et al Mol Imaging Biol. 2005; 7(5):342-50
5. Dumbell et al Front Endocrinol (Lausanne). 2016; 7:37

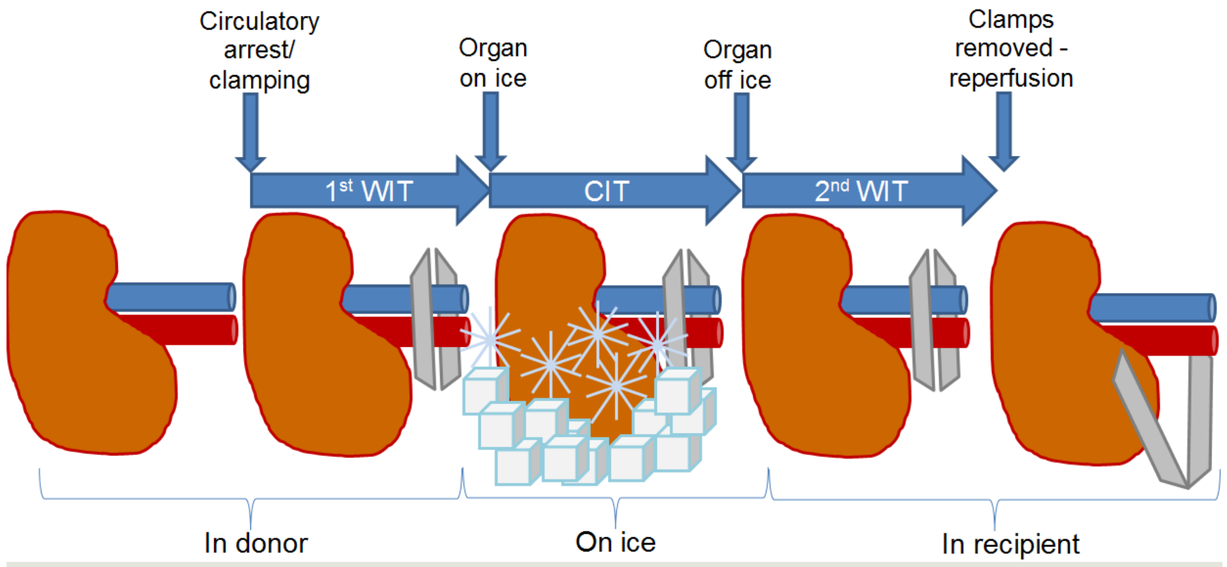
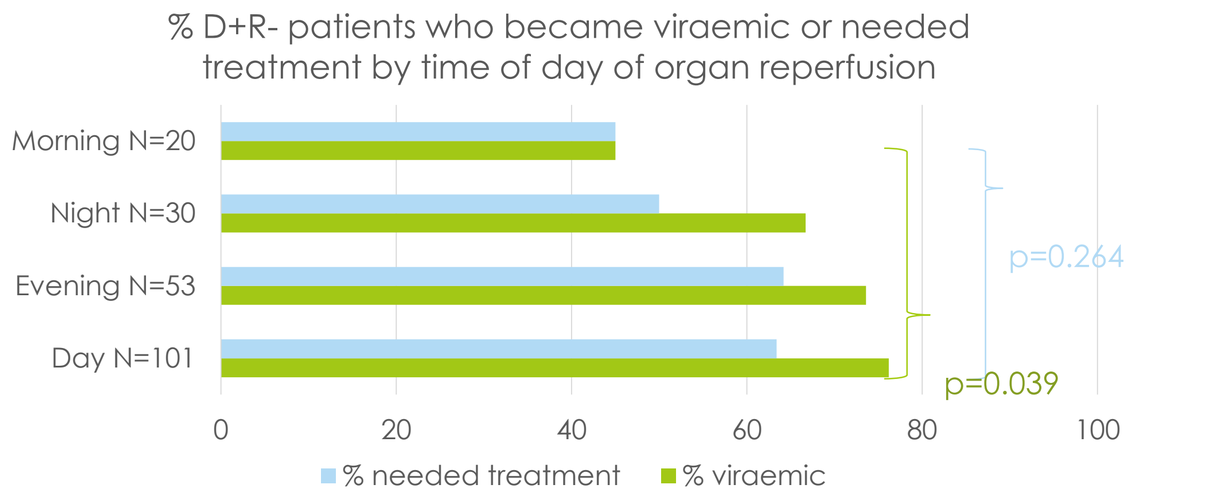


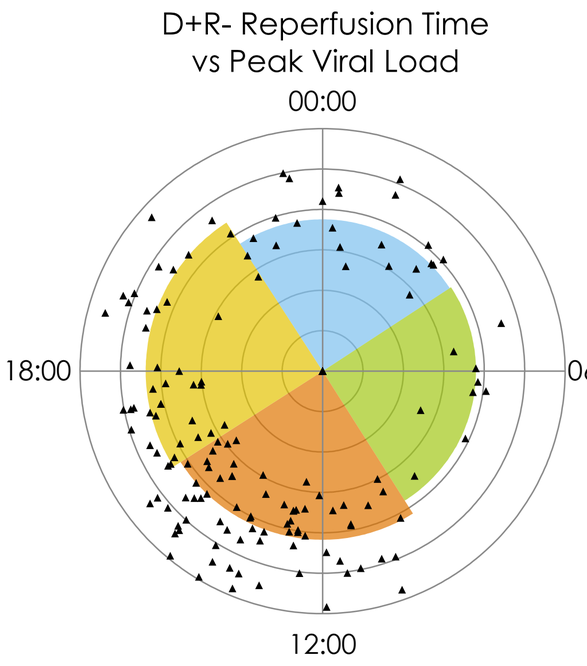
Figure 2 showing times recording during transplant surgery. 1st warm ischaemia time (1st WIT), Cold ischaemia time (CIT), 2nd Warm ischaemia time (2nd WIT)

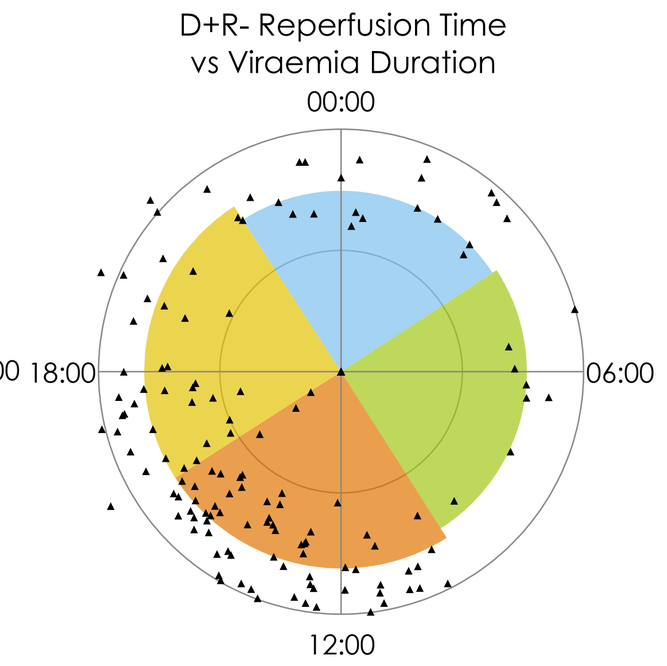
Results

- 788 transplant patients included (397 renal, 391 liver)
- Median age 51, 37.3% recipients and 46.1% donors female
- Data analysed with STATA 13 using Kruskal-Wallis test for p-values
- No significant associations between virological parameters and age, sex, CIT, or 1st/2nd WIT
- There were no significant associations for the D-R+ or the D+R+ groups or for time of cardiac arrest of donor



For D+R- group Reperfusion time Among those that developed viraemia		Day 10am – 4pm N=101	Evening 4pm-10pm N=53	Night 10pm-4am N=30	Morning 4am-10am N=20	P value
Peak viral load, Copies/ml	Median (IQR)	14870 (3220-97551)	23789 (3509-58314)	5685.5 (2711-26407)	6238 (2839-8131)	0.074
Duration viraemia, Days	Median (IQR)	42 (24-63)	42 (18-70)	31 (21-57)	34 (26-35)	0.555
Duration treatment, Days	Median (IQR)	48 (33-64)	47.5 (29-67)	42 (29-66)	28 (21-41)	0.257





Conclusions

- Time of day of organ reperfusion associated with development CMV viraemia in D+R- patients with highest viraemia in the day – as hypothesized
- Possibly explained by circadian rhythms of CMV and varying immunological parameters throughout the day

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