Four-day continuous blood exposure leads to prolonged joint damage in a canine *in vivo* model, whereas intermittent blood exposure does not

MER van Meegeren,[1,2] G Roosendaal,[2] K van Veghel,[1,2] NWD Jansen,[1,2] FPJG Lafeber[1], and SC Mastbergen[1]

University Medical Center Utrecht

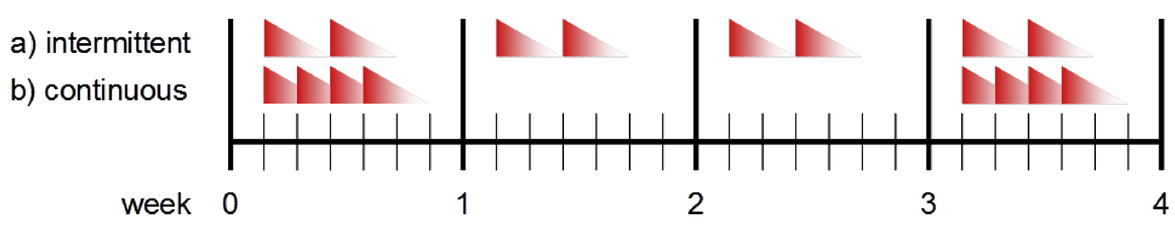
[1]Rheumatology & Clinical Immunology, University Medical Center Utrecht, The Netherlands
[2]Haematology and Van Creveld Clinic, University Medical Center Utrecht, The Netherlands

Introduction

Exposure of cartilage to blood can occur after joint trauma, during or after major joint surgery, or in hemophilia patients. This ultimately leads to joint damage, having both the inflammatory characteristics of rheumatoid arthritis and the degenerative characteristics of osteoarthritis. It was shown *in vitro* that exposure of human and canine cartilage to 50% v/v blood for 4 days leads to irreversible inhibition of cartilage matrix synthesis. In humans the natural evacuation time of blood from a joint is considered to be 4 days. In dogs however, it appeared that the evacuation time is much shorter; within 2 days blood load decreases to less than 5% v/v. It has also been shown *in vitro*, that 2 days exposure of at least 10% v/v blood is needed to induce irreversible cartilage damage. As such, Beagle dogs injected intra-articular with autologous blood twice a week during 4 weeks did not develop permanent joint damage. This tempted us to compare equal blood loads by a) intermittent injections mimicking quick aspiration from the joint after each bleed and by b) daily injections mimicking a continuous blood exposure as seen upon a human joint bleed (see schematic overview on the right).

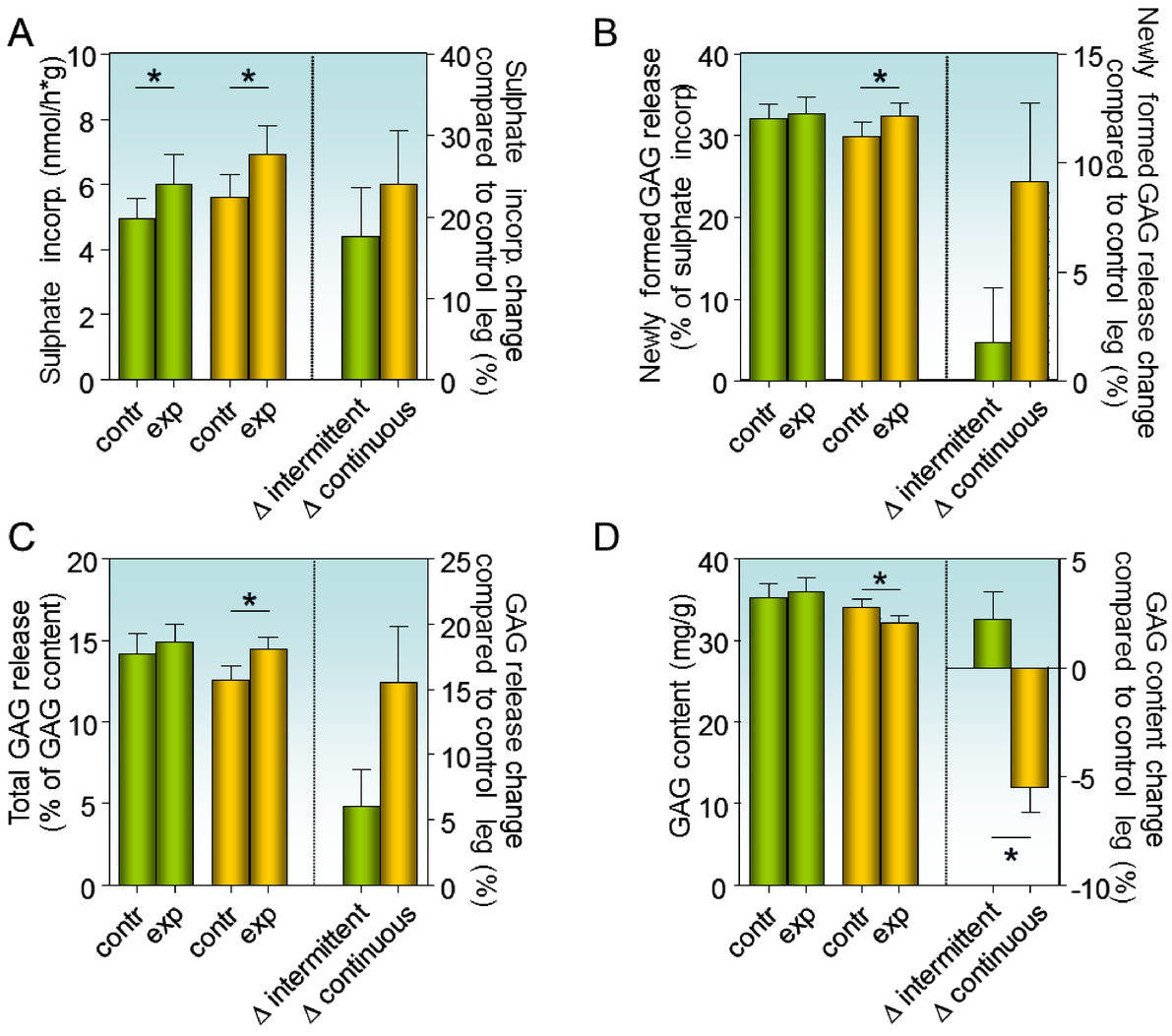
Methods

Fifteen skeletally mature Beagle dogs, mean age 2.1 ± 0.1 years, weighing 9-15 kg were used. In 7 dogs left knees were injected intra-articular with freshly collected autologous blood twice a week during 4 weeks, with at least 2 days in between to induce intermittent blood-exposure. The contralateral knee of these dogs served as a control. In the other 7 Beagles left knees were injected for 2 periods of 4 consecutive injections leading to 2 continuous blood loads with more than a 2 week interval over a period of 4 weeks (scheme below). To check for possible synovial inflammation by repeated intra-articular injections, in this group the right knees were injected at the same frequency with an equal volume of saline. Ten weeks after the last blood-injections changes in biochemistry of cartilage were determined and inflammation of synovial tissue was evaluated macroscopically.



Results

Figure 1 Biochemistry of blood injected knee joints



- There was no difference in proteoglycan turnover (figure 1A-D) and synovial inflammation (figure 2A and 2C) between the control legs of both groups (non-injected versus saline-injected joints).
- In the blood-exposed joints of both groups proteoglycan synthesis rate was increased, suggesting repair activity of the cartilage (figure 1A; $p<0.05$). However, the increased proteoglycan synthesis was ineffective in the continuous prolonged blood-exposed knees, since the release of newly formed GAG release was increased in this group (figure 1B; $p<0.05$). Furthermore, the total release of proteoglycans (primarily resident proteoglycans) was increased in case of continuous prolonged exposure (figure 1C; $p<0.05$) but not in case of intermittent short-term exposure. Ineffective synthesis and enhanced release led to a statistically significant (figure 1D; $p<0.05$) decrease in proteoglycan content in case of continuous prolonged exposure but not in case of intermittent short-term exposure. Moreover, the relative change in proteoglycan content compared to the control leg was statistically significant lower after continuous prolonged exposure than after intermittent short-term exposure (right panel of figure 1D).

Figure 2 Macroscopic synovial inflammation

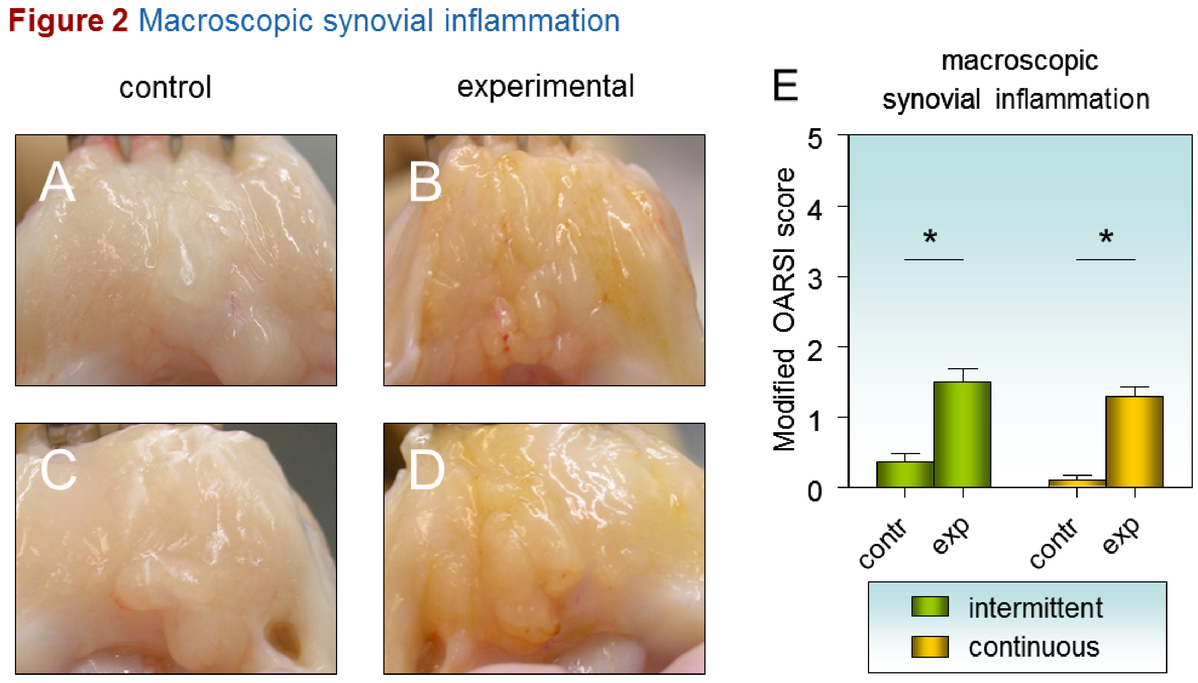


Figure 2 shows representative pictures of synovial tissue of intermittent short-term blood-exposed knees (figure 2B) and after continuous prolonged blood-exposure (figure 2D). Mild synovial inflammation was observed due to blood injections, statistically significant for both groups (figure 2E; $p<0.05$). There was no difference in synovial inflammation between the two groups.

Conclusion

In this canine joint hemorrhage model it is shown that a 2 times 4-day continuous exposure of a joint to blood, and not intermittent short-term exposure of a same blood load (total cumulative volume injected over time), leads to persistent cartilage damage in terms of proteoglycan turnover. These effects are independent of the degree of synovial inflammation. This implies that the duration of blood exposure is more important than the cumulative blood load for the induction of long-lasting cartilage damage. As such, quick aspiration of a joint after a joint bleed will protect the joint from blood-induced damage.

Acknowledgements

This study is financially supported by an unrestricted grant of Baxter.

Rheumatology & Clinical Immunology, F02.127, University Medical Center Utrecht
PO Box 85500, 3508GA, UTRECHT, The Netherlands

email: m.e.r.vanmeegeren@umcutrecht.nl;
f.lafeber@umcutrecht.nl
website: www.umcutrecht.nl/rheumatology-research

WFH2012
218-We
Musculoskeletal Issues
Monique van Meegeren
DOI: 10.3252/pso.eu.WFH2012.2012
Poster presented at: WFH 2012 World Congress
PosterSessionOnline.com