LETTER TO THE EDITOR

Does size matter?

To the Editor:

In recent years, there have been important advances towards clinical application in the use of pig cells, tissues or organs for the treatment of organ failure. These include the generation of pigs with multiple genetic modifications and the introduction of new immunosuppressive regimens, both to prevent rejection, and also the development of new sensitive detection methods and elimination programs to prevent the transmission of porcine microorganisms. At present, pig islet cells can maintain insulin-independent normoglycemia for a maximum of 950 days in diabetic monkeys, the maximum survival time for the heterotopic transplantation of pig hearts to non-human primates has increased to 945 days and in the field of kidney transplantation, three groups have achieved greater than 6-month survival. A maximum survival of 90 days in orthotopic heart transplantation has been achieved recently.

However, it is still unclear whether the difference in the sizes of pig organs and non-human primate organs may contribute to earlier transplant failure. This problem is obvious when one considers that an adult pig at slaughter weighs 110-125 kg and a baboon only 10-30 kg. Abicht et al. reported an enlargement of porcine intrathoracic cardiac xenotransplants in baboon recipients. An increase in the size of kidney xenotransplants from pigs with three genetic modifications was also reported and this was not a result of rejection. The opinion that increase in organ size is associated with rejection had its origin in a publication, in which the authors showed that pig kidneys increased in size considerably before rejection after only 4 weeks. However, when thymokidneys from alpha1,3-galactosyltransferase gene-knockout (GalTKo) pigs were transplanted to baboons, the most striking finding was the growth of the transplant after 12 weeks without any sign of rejection, which was similar to what was observed in a pig. When Yorkshire pig kidneys were transplanted into miniature swine and in parallel kidneys from miniature swine were transplanted into miniature swine, the Yorkshire transplant grew more rapidly compared with the control miniature swine kidney, indicating that factors from the donor organ were responsible for growth.

It is important to note that heterotopically transplanted hearts in the abdomen have more space compared to orthotopic heart transplants. This may explain the difference in the survival time between heterotopic and orthotopic transplantations (90 days in orthotopic vs 945 days in heterotopic transplantation).

Analysis of the heart and body weights of humans, pigs and non-human primates is important to explain the differences. The ratio of heart weight to body weight in 20- to 30-kg pigs is identical (5 g/kg) to that of adult humans. A study of humans with an average age of 24 years found heart weights of an average of 331 g (men) and 245 g (women). Another study found hearts with 267 g in humans and 303 g in pigs. Although the size of pig hearts appears to be suitable for humans, in the case of non-human primates, it would seem reasonable to use organs from minipigs. In Göttingen minipigs, the mean heart weight in 8-week-old pigs is 20-23 g, in 6-month-old pigs 60-74 g. However, in transplantations using minipigs, these animals should have the same genetic modifications as the animals generated for use in humans.

In conclusion, in addition to immunological rejection, the size of the transplants may influence the survival time of xenotransplants in non-human primates. The use of minipigs or pigs with mutations in the gene of the growth hormone receptor may overcome these problems.

ACKNOWLEDGMENTS

We would like to thank Dr. M.-J. Abicht, Ludwig-Maximilians-Universität, Munich for fruitful discussions on the topic, and Dr. S. Norley, Robert Koch Institute, Berlin for critically revising the manuscript. This work was supported by the DFG Sonderforschungsbereich Xenotransplantation, TRR127.

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REFERENCES


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