Determining the Rate of Growth of a Pig Organ in a Primate

Peter J. Friend and Bob Soin

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For many good reasons, most of the research effort in xenotransplantation has been directed to the immunological problems, particularly those encountered in the discordant species combination of pig-to-primate, which is widely regarded as the most relevant for future clinical application. The success of strategies to circumvent hyperacute rejection, namely the production of animals transgenic for human complement regulator genes, has now enabled medium-term graft survival. This has allowed the study of some of the many parameters of physiological compatibility, which will be critical if xenotransplantation is to become an effective therapy.

Regulation of Organ Growth

The growth of an organ is regulated by various factors and is poorly understood. The size attained by an organ is likely to be influenced by local and systemically-acting growth factors, as well as direct genetic factors. It is also clear from physiological and anatomical observations in clinical practice that the size of an organ is partly affected by demand. In a patient who undergoes unilateral nephrectomy as a living organ donor, the function of the remaining kidney will increase to provide substantial compensation.[1]

The growth of an organ transplanted across species may be inappropriate for the size and needs of the recipient for several reasons. First, the organ may, even in the absence of hormonal influences, be genetically predetermined to be of a different size. Second, the xenotransplanted organ may not respond to the local and/or systemic growth factors of the recipient.

Comparison of Pig and Human Organ Size

The vascular anatomy of the porcine kidney and heart vary in a similar way to the comparable human organs, and these variations should not represent a limitation in clinical xenotransplantation of these organs. The size (in terms of body weight) of domestic adult pigs is considerably larger than that of adult humans. The volume of the donor organ must not be too great for the recipient at the time of transplantation or grow subsequently to become too big for the body cavity in which it is contained. This is illustrated in Figure 1, where pig heart and liver weights and volume are plotted for pigs of body weight up to 110 kgs. A healthy adult human heart weighs between 200-300 g and an adult human liver between 1300-1500 g, which are comparable to those in a weight-matched pig but substantially less than than those for larger fully-grown pigs. Thus, there is the risk that the large size of porcine donor organs will cause problems after clinical xenotransplantation if growth regulation, appropriate to the size of, and demands imposed by, the recipient, does not occur.

When considering the cross-species function of growth factors, most is known about growth hormone. In vitro studies have demonstrated species restriction of the action of this hormone. However, this operates in a unidirectional manner—although porcine growth hormone cannot activate primate growth hormone receptors, primate growth hormone does activate porcine receptors. This appears to be a function of a single amino acid difference at position 171.[2] Such isolated experiments must be interpreted with caution, however, because of the complex interactions which occur between growth hormone and other molecules involved in growth, including somatomedins.[3]

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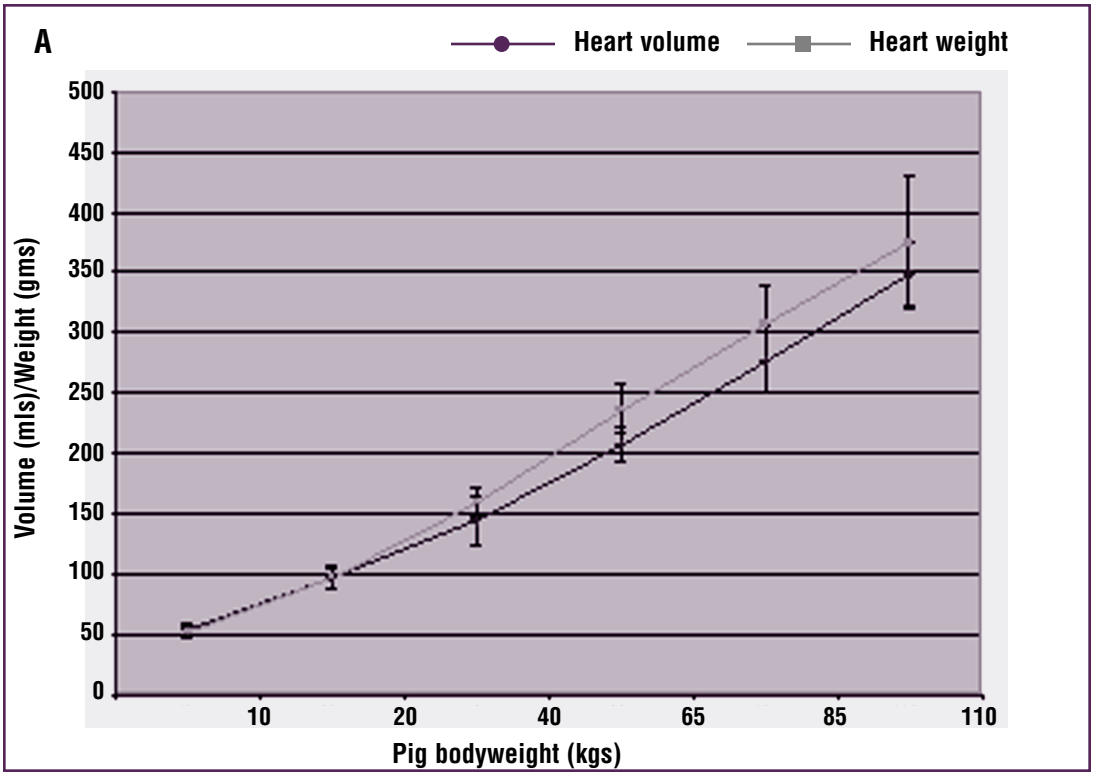

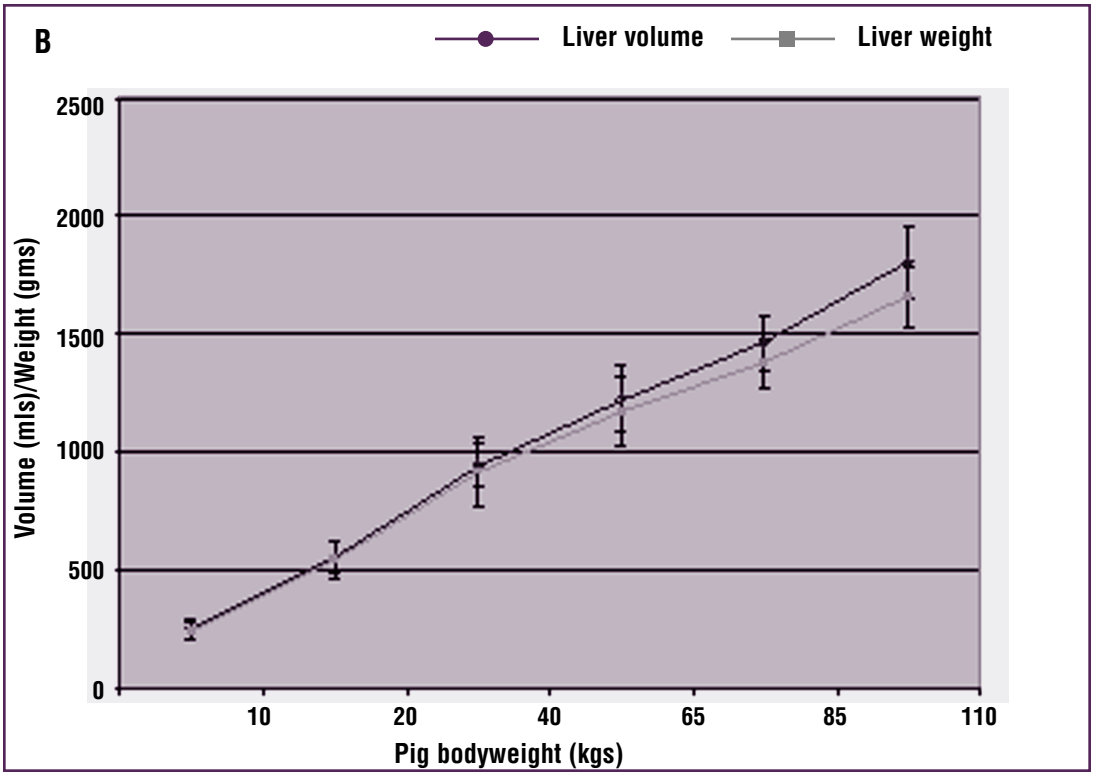

Figure 1. Heart (A) and liver (B) weight and volume by increasing pig body weight (original data).

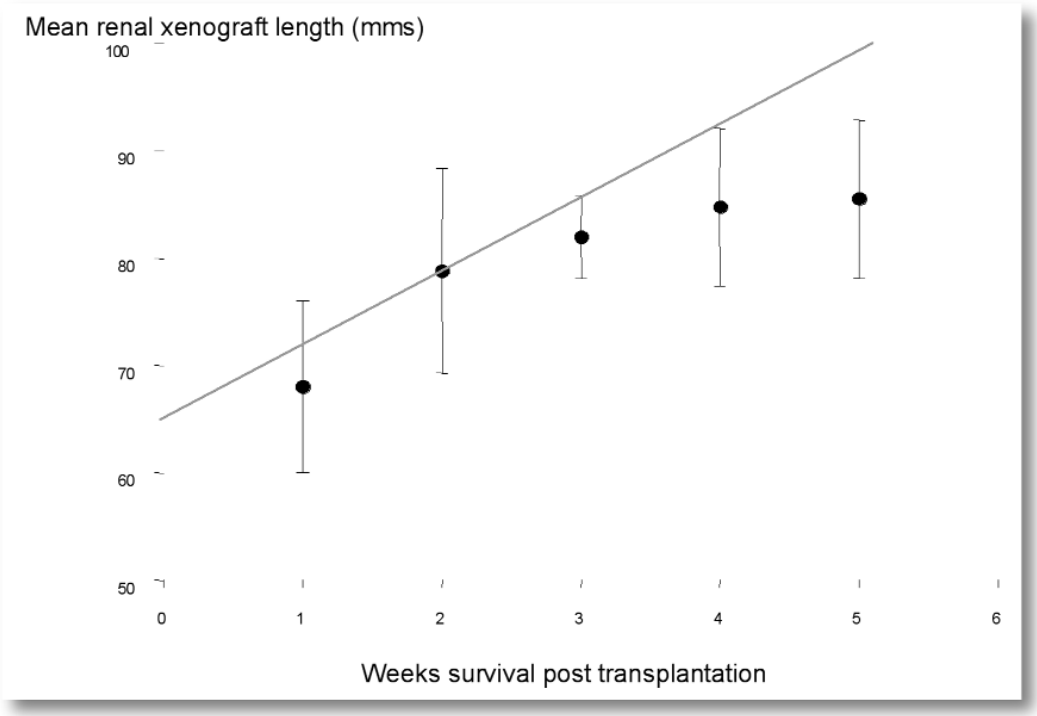

Figure 2. Growth of xenotransplanted renal xenografts by week (mean ± 1 s.d.).

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Studies in the Pig-to-Primate Preclinical Model

Studies with pigs transgenic for human decay accelerating factor have enabled some simple, but possibly important, observations to be made in respect of the growth of porcine organs in a primate environment. Life-supporting renal xenotransplantation has been carried out in sufficient numbers and with survival for a long enough period of time to enable sequential measurements to be made of kidney size. By contrast, the majority of cardiac transplants in the same or a similar model have been heterotopic and, therefore, non-working. Much smaller numbers of orthotopic cardiac transplants have been carried out, and these have been followed by a mean survival that is too short to allow a definitive interpretation of the rate of growth.[4] It should be noted, however, that the renal xenotransplant model involved the transplantation of a kidney of a very young (less than one month) pig into an older cynomolgus monkey of 3-4 kg.[5] In a clinical environment, the kidney of a much more mature pig would be used and may express different growth characteristics.

The growth of transplanted pig kidneys has been compared by serial ultrasound measurements to that of untransplanted kidneys in pigs of the same age and size as the donor animals. After transplantation, there is an initial rapid rate of growth of the xenotransplanted kidney, similar to that in the pig. At about two weeks, the growth rate drops below that in the pig (Fig. 2); whether this is due to a lower level of (primate) growth hormone or lower metabolic demand in a smaller host is not clear. These data are also complicated by the development of rejection at various time points; this causes edema and can be misinterpreted as growth. However, if the measurements are taken only at autopsy, the rejecting kidneys can be excluded from the analysis (Fig. 3).

An alternative approach to the question is to look at the maximum size achieved by the kidney during the natural life of the pig. Post-mortem studies of kidneys removed from pigs of different sizes suggest that the size of the kidney reaches a plateau at approximately 170 g, and this is reached at about 8 months of age or more. The weight of the kidney from a pig of a similar body weight to an adult human is, therefore, approximately equal to the weight of a normal adult human kidney (120-140 g).

With the opportunity of carrying out xenotransplantation in a clinically relevant large animal

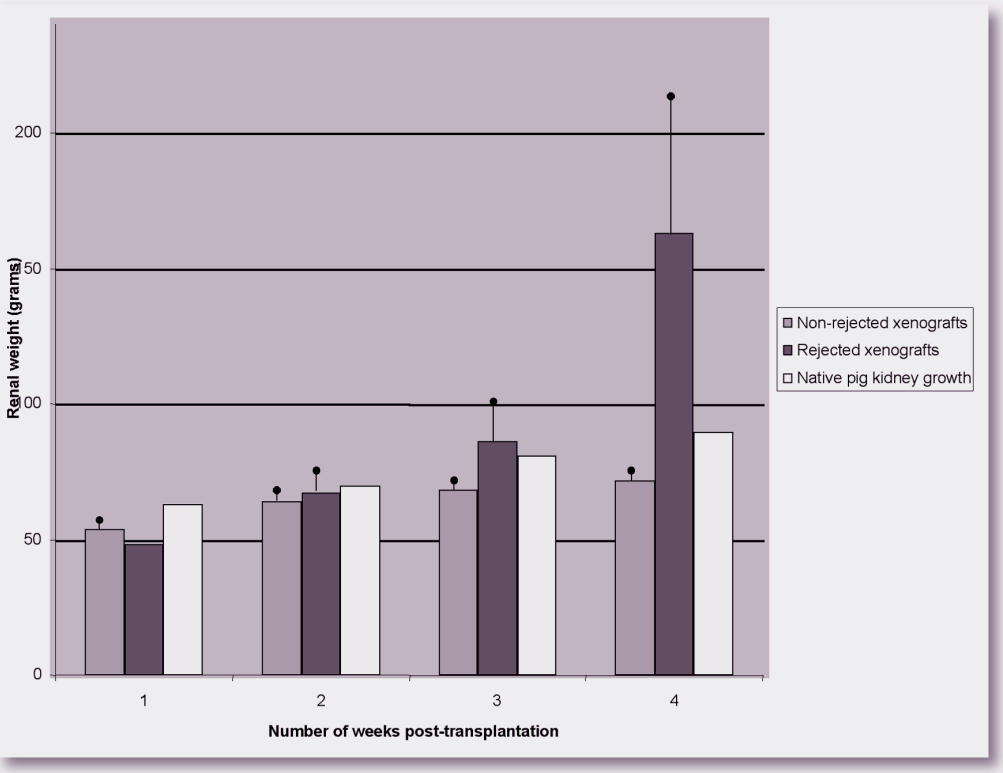

Figure 3. Correlation between xenograft weight and rejection.

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model, much work remains to be done to investigate the issue of growth. However, although it may be possible to study in more detail the hormonal and genetic control of growth, it is likely that the questions will not be fully answered until long-term preclinical experiments or clinical trials of xenotransplantation are carried out.

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