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Selection criteria for liver donation: a review

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Abstract. An overview of the criteria that are currently being used for the selection of liver donors is presented. The validity of the different criteria is discussed. The potential benefits of introducing other modalities is dealt with.

Key words: Liver transplantation, donor criteria – Selection, livers for transplantation – Viability, donor liver – Magnetic resonance spectroscopy, liver donor selection

Introduction

Ideally, parameters reflecting the condition of a donor liver should show a correlation with final transplant outcome. However, such a correlation has not yet been established. The ability of the currently used selection criteria for liver donation to predict transplant outcome is the subject of great controversy at different experienced transplant centers. This controversy is not merely academic. There is a rapid increase in the number of patients on waiting lists for different organs, while the supply of available organs is increasing only slowly [88]. For liver transplant candidates this means a high mortality rate: one in four to five patients will die while awaiting a transplant [5, 17, 109]. Pediatric donors are especially hard to find, and the mortality for candidates in this age group is even higher: one in three [17].

The discrepancy between the number of candidates awaiting transplants and the number of available organs is largely attributed to the fact that a considerable number of potentially suitable organs are not harvested. In a substantial number of cases potential donors are not used because they do not fulfill predefined selection criteria [35, 36]. In the years 1988–1990, about 40% of the donor organs offered to the Eurotransplant Foundation were turned away by transplant centers on medical grounds [88, 93]. Centers tend to adhere strictly to their selection criteria because they fear accepting and transplanting livers of poor quality may result in severe complications and primary nonfunction (PNF) [73]. In the latter case, patients will either die or have to be retransplanted, resulting in a decreased patient survival [17, 56, 110] and an increase in the costs of the procedure [56]. Moreover, the need for an additional liver for the same patient places added pressure on those already on the waiting list, i. e., more patients remain on the waiting list for a longer period of time. The increased waiting time is likely to result in an aggravation of the candidates' condition and, consequently, their chances for success will be reduced.

A primary question in liver transplantation is whether rejecting donor organs on the basis of often nonvalidated criteria is justified. It is not difficult to imagine that because of the absence of reliable selection criteria, good livers are presently being turned away while bad livers are being accepted for transplantation. Both scenarios are undesirable. Therefore, an assessment of the validity of different criteria for liver donation is urgently needed.

Suitability for liver transplantation is determined on the basis of two kinds of criteria: those used to evaluate the condition of the donor in general and those used to evaluate the condition of the liver itself. In this paper, we will focus on both of these. Other obvious criteria, such as the presence of transferable diseases (e. g., cancer) or primary organ diseases (e. g., cirrhosis) in the donor will not be discussed.

The liver donor

Infections in the donor, viral

Livers of anti-HIV and HbAg-positive donors should not be used because they imply the transfer of the virus to the recipient [113] or transplantation of a diseased organ with the potential for malignant degeneration [8].

The hepatitis C virus (HCV) has caused a lot of controversy lately with regard to transplantation. HCV is as-

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sociated with various conditions including chronic active hepatitis, liver cirrhosis, and hepatocellular carcinoma [61]. HCV infection is thought to be responsible for 60% of transfusion-associated non-A non-B hepatitis in 5%–12% of all recipients of donor blood transfusions in the United States [1]. Reports on virus transmission through kidney transplantation [83], bone marrow transplantation [64], and after infusion of contaminated immunoglobulin [27] have been published. In a retrospective study, Pereira et al., from the New England Organ Bank, questioned the use of donors testing positive for HCV [87]. Organs from 12 anti-HCV-positive donors were transplanted, a total of 29 organs in 29 recipients. Seven of the recipients were already anti-HCV-positive before the transplantation. Hepatitis C developed in 14 recipients receiving organs from 9 of the 12 HCV-positive donors; the mean time was 3.8 ± 1.5 months between transplantation and development of hepatitis. During the follow-up of these recipients, eight showed chronic active hepatitis or cirrhosis in their liver biopsies. Based on these findings, the New England Organ Bank has adopted a policy of limited use of anti-HCV-positive donors in the case of life-saving transplantations (liver, heart, lungs) and exclusion of anti-HCV-positive donors in the case of transplantation of other organs (kidney, pancreas). Members of the Southeastern Organ Procurement Foundation and the United Network for Organ Sharing (UNOS) adopted a similar policy [71]. However, these policies are heavily debated [26, 90]. Arguments used in the discussion are the organ shortage, the uncertainty as to whether the virus came from the donor or from the blood transfusions given to the recipient, and the limited sensitivity and specificity of the available tests for anti-HCV. In addition, antibodies to HCV appear in the circulation between 1 and 3 months (and in rare cases, not until a year) after the onset of acute illness, often resulting in false-negative serology [6, 111].

Based on these considerations, a first step towards reducing HCV infection after transplantation should be the introduction of obligatory testing for anti-HCV in each organ donor. Because of the implications of HCV infection in the recipient, anti-HCV-positive donors should not be used in kidney and pancreas transplantation. The observed low frequency of the virus in the population allows for such a policy. The use of anti-HCV-positive donors in heart, liver, and lung transplantation should be based on the urgency of the need for a graft.

Members of the herpes virus family, e.g., cytomegalovirus (CMV), Epstein-Barr viruses (EBV), and varicella zoster virus (VZV) are ubiquitous agents that infect almost all human beings at some point during their lives (prevalence of anti-CMV antibodies in adults 35%–80% [99]). Consequently, a considerable number of organ donors will be positive for one or more of these viruses.

Infection with CMV from the transplanted organs has been proven both in kidney transplantation [21] and in liver transplantation [37, 41, 66]. Although CMV infection ultimately did not change survival or liver function, morbidity was high. Complications may include graft dysfunction due to viral hepatitis [19], pulmonary dysfunction [115], and gastrointestinal disorders [105, 116]. CMV hepatitis may also mimic allograft rejection and lead to inappropriate immunosuppressive therapy [104]. Finally, it has been hypothesized that the virus may cause an upregulation of MHC antigens, inducing rejection [104, 133]. Donor-recipient matching for CMV has proven to be worthwhile in elective patients, reducing the incidence and complications of post-transplant CMV infections [69, 86]. Even CMV-positive patients can profit from a CMV-negative donor liver because the liver is the main source of transmission of the virus. Such donor-recipient combinations have a lower incidence of CMV infection than CMV-positive donor/CMV-positive recipient combinations [33, 41, 97]. Disadvantages of this policy include the need to use CMV-negative blood products in cases of negative donor/negative recipient combinations. However, since blood donors outweigh liver donors, the logistics do not cause major problems [76, 114]. Furthermore, the waiting time increases, so the decision to adopt the policy for a particular recipient should be balanced against the need for a new liver.

Another virus from the herpes group that may cause concern is the Epstein-Barr virus (EBV). Recently, Telenti et al. described two cases in which recipients received livers from donors that were serologically positive for EBV. Both recipients experienced a primary infection 1.5 years after transplantation, with asymptomatic worsening of the liver tests as the major manifestation. Tapering of the immunosuppression and administration of acyclovir proved to be an effective treatment [122]. It was suggested that EBV can be transferred via the transplant organ. Due to the long interval between transplantation and the occurrence of the symptoms, however, this cannot be confirmed. Langnas et al. recently described their experience with viral hepatitis due to EBV. Although the incidence of EBV infection was low in their series (10 of 668 patients), complications were grave as two subjects progressed to systemic disease and subsequently died [59]. In our own experience with pediatric transplantation, 12 out of 32 transplanted patients seroconverted, with some patients showing extremely high viral capsid antigen titers. Only one of the patients showed clinical symptoms of EBV infection. A major concern is that in a small percentage of cases, an EBV infection will progress to the occurrence of malignant lymphomas in these immunosuppressed patients [9, 43, 140]. On the other hand, a reduction, or even disappearance, of the tumors has been noted after tapering of the immunosuppressive therapy [117]. Consequently, because of the low incidence of major sequelae, the EBV status of a donor is not a major consideration when deciding whether to accept or discard a donor liver, except in the case of an active EBV infection (infectious mononucleosis) in the donor at the time of death.

Infections with varicella zoster virus (VZV) – chickenpox – are usually benign and occur in childhood. They can, however, cause serious infections in immunocompromised patients. As reported by Wreghitt et al., four out of five Cambridge kidney transplant recipients who acquired a primary infection died as a result of it, even though three were treated with acyclovir [136]. Primary VZV infection can produce a disseminated infection characterized by hemorrhagic pneumonia and skin lesions, encephalitis, disseminated intravascular coagulation, and

hepatitis [104]. Therefore, in the case of an active and systemic VZV infection, organ donation should not be considered. In other cases, transfer of the virus will be unlikely.

Infections in the donor, bacterial

Symptoms suggestive of septicemia in a potential organ donor are an absolute contraindication for donation. However, there are some possible exceptions to this rule. In children, meningitis caused by *Hemophilus influenzae* or *Neisseria meningitidis* and leading to brain death often coincides with septicemia. Provided the pathogen has been identified, its resistance pattern to antibiotics identified, and an adequate response to antibiotics seen for at least 24 h before organ retrieval, these children can be considered as organ donors. Inclusion of the right antibiotics in the therapeutic regimen of the recipient will provide additional protection from infection in the recipient.

Localized bacterial infections that do not involve the organs to be harvested are not an absolute contraindication for organ donation, provided contamination of the explanted organs is avoided. Often organ donors stay in the intensive care unit for several days, and during this period they are colonized with often highly pathogenic bacteria [7, 118]. Donor teams should be aware of this phenomenon since transfer of the bacteria may cause serious infections in the immunocompromised host. A preventive measure would be to take cultures from skin, oropharynx, and anus in order to identify these pathogens and, if necessary, to incorporate the right antibiotics into the antibiotic regimen of the recipient.

Age of the donor

In an extensive review, Popper has dealt with the influence of aging on the structure of the liver, hepatic function, and hepatic macromolecules [92]. It is clear from the review that the aging of the liver as such does not lead to an overall decreased functional capability, and Popper gives three explanations: the liver's great functional reserve, its regenerative capacity, and the ample blood supply to the liver, which far exceeds its needs. Therefore, strict adherence to an upper age limit for liver donation is debatable.

Wall et al. compared the function and outcome of liver grafts from "older" donors (> 50 years) with grafts from younger donors [127]. In their experience, graft function – as determined by peak aminotransferase levels, duration of prolonged prothrombin time, retransplantation rate within 30 days, and incidence of primary nonfunction – was not significantly different in older and younger grafts. Actuarial 1-year graft and patient survival rates were 65 % and 71 %, respectively, in recipients of older grafts and 69 % and 76 %, respectively, in recipients of younger grafts. Differences were not statistically significant. Mor et al., in a series of 365 donor-recipient combinations, also were unable to identify age over 50 years as being a risk factor for poor graft function [72]. Others have confirmed these findings for livers up to 65 years of age [2, 23, 123]. In contrast, Greig et al. reported a negative influence of donor age on final transplant outcome [38]. Similar trends were seen in the European CLTS Registry. Transplantations performed with livers from donors over 60 years of age showed a poorer graft survival than those performed with livers from younger donors (Opelz, personal communication). The UNOS experience with 2913 liver grafts showed that recipients of donor livers aged 16–45 years had an 11 % better 1-year graft survival than recipients of donor livers over 45 years of age. However, the differences disappeared when corrected for the age of the recipients. Consequently, the effect can probably be attributed to a greater percentage of high-risk and older recipients being transplanted with livers from older donors [5]. Ploeg et al., in an analysis of their donor population ($n = 330$), also reported donor age over 50 years (among other factors) as being a risk factor for poor liver function after transplantation [91].

The problem with the studies cited is that all were of a retrospective nature and/or nonrandomized: the livers from elderly donors were not randomly allocated. Moreover, graft quality was determined by many factors. As a result, the debate about the upper age limit continues. Empirically, however, donors up to the age of 50, and perhaps even above, seem to be able to provide well-functioning liver grafts in selected donors and recipients.

At the other end of the age spectrum, there is a reluctance to use neonatal donors, based on the immaturity of their liver. The capacity for bile-salt synthesis increases with gestational age, and both the infant cholate pool and the synthetic rate are significantly lower than in adults [40, 129, 130]. Adult levels of cholic acid and chenodeoxycholic acid are found at 3–6 months of age [47]. Greig et al. showed an increased risk of poor post-transplant liver function in younger child donors [38]. Recently, the Pittsburgh group also published their experience with the use of neonatal (< 28 days) donor livers as compared to older infant donors. Although differences did not reach statistical significance, graft survival at 1, 2, and 3 years was considerably less (56 %, 56 %, and 38 %, respectively) than in the older group (76 %, 76 %, and 74 %, respectively). In addition, it was found that bilirubin clearance was significantly less in the neonatal donor group [139]. These observations would lead one to the conclusion that infants below 3 months of age should not be used as liver donors. When doubt exists, bile acid levels should be measured in very young donors to estimate the maturity of the enterohepatic circulation of bile acids.

Length of hospital stay of the donor

The length of the hospital stay of the donor is a factor that shows a negative correlation with the final success of the procedure. A retrospective study by the European Liver Registry demonstrated that livers from donors hospitalized for over 5 days showed a higher risk of primary nonfunction (PNF) than livers from donors hospitalized for a shorter period [95]. Similar observations were made by other groups [38, 91, 138]. This observation may well be an

indication of an underlying phenomenon, and the nutritional status of the donor has been suggested as being one such phenomenon. Donors are often malnourished. On the one hand, this is due to a policy fluid restriction to combat brain edema while, on the other hand, these patients may often not be fed properly because of their poor prognosis. Boudjema et al. were able to show in the pig model that liver viability after preservation was reduced in livers coming from animals that had fasted [13]. This loss of viability is attributed to glycogen depletion in order to maintain normoglycemia. In humans, too, fasting leads to glycogen depletion [77, 119]. When glycogen-depleted livers are being harvested and high-energy phosphates (ATP) are being used during warm and cold ischemia, the substrate for recuperating these high-energy phosphates, i.e., the glycogen, is exhausted. Different authors have shown that the ability of a donor liver to function properly after preservation and transplantation depends on its ability to regenerate ATP [44, 53]. In the current situation, hospitalization of a donor for over 5 days coincides with an increased risk of PNF. Awareness of this phenomenon is important in the process of donor selection.

Hypotension and cardiac arrest

A great number of donors experience periods of hypotension or even temporary cardiac arrest. This may be caused by the trauma inflicted or may be due to the hemodynamic instability that is observed after the occurrence of brain death. Moreover, it may be enhanced by fluid restriction for the treatment of cerebral edema. The insufficient circulation causes a sequence of events at the cellular level that eventually cause cell death, among them: deterioration of membrane function, stimulation of Na/K ATPase with ATP depletion, decline of cyclic AMP levels and alteration of the responsiveness of the adenyl cyclase system, uncoupling of the cytochrome electron system and, eventually, the release of lysosomal enzymes [20]. Moreover, hypovolemic shock may lead to fatty degeneration of the liver, as was shown in the pig model [58], and to central lobular necrosis, as was shown in patients with severe shock of different origin [62].

Unfortunately, data indicating the acceptable duration and extent of insufficient circulation are not readily available. In rats, the former was found to be 60–120 min [45, 51], although ATP levels do not return to preshock values [11]. In humans, findings from other fields of liver surgery have shown that the liver is relatively resistant to warm ischemia: a complete vascular occlusion of the liver in normothermia can be extended up to 50–60 min without functional consequences after the operation [10]. Whether these data also apply to the liver transplant situation is doubtful because of the additive effects of ischemia/hypovolemia, malnutrition, and cold ischemia. Empirically, donors who have experienced prolonged and/or severe hypotension or repeated cardiac arrests can be accepted for liver donation provided a sufficient recuperation period (12–24 h) has followed the event(s). Circulation should be stable and, as a reflection, adequate diuresis should be restored. Future research in this field is urgently needed.

The donor liver

Liver biopsies

Using liver biopsies to assess the quality of the donor liver is a very old practice within the field of liver transplantation. In 1984 Rolles and Calne reported a case with severe fatty degeneration of the hepatocytes in the biopsy and a fatal outcome after the transplantation [102]. Recent studies from the Philadelphia and Wisconsin groups confirm the importance of fatty degeneration. They were able to show the detrimental effects of steatosis in the biopsy on final transplant outcome [24, 75]. In a more empirical way these observations are confirmed by others [2, 81]. As a result of these findings, livers with severe fatty infiltration should not be used for transplantation. Whether minor fatty infiltration also has a negative effect on transplant outcome needs to be explored further.

Laboratory data

The serum enzyme levels often used to accept or to discard a donor liver are lactic dehydrogenase (LDH), Aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Strictly speaking, the activity of these enzymes reflects cell damage – not synthetic capacity – and is not specific for the liver. In the donor situation these enzyme levels may reflect trauma to other organs and tissues as well. In a nontransplant situation these enzyme determinations, when used alone, have limited discriminative capacity as to different types of liver diseases [134].

Both Makowka et al. and Burdelski et al. questioned liver enzyme determinations and other routine laboratory data as selection criteria for liver donation in retrospective studies [16, 65]. The first group was unable to find any differences in the results of a group of recipients receiving "good" livers and those receiving "bad" livers, good and bad being defined on the basis of liver enzyme determinations and hypotension. Burdelski et al. found no correlation between donor AST serum levels and the performance of the graft. In a retrospective study we were able to confirm these observations, with the possible exception of the gamma glutamyltranspeptidase (GGT). In this study the GGT of the donor showed a correlation with graft survival up to 1 year after transplantation [94]. This latter finding may be relevant since a raised GGT is, among other things, an indication of fatty degeneration of the liver [55]. D'Allesandro and Moritz, in separate studies, both indicated the detrimental effect of steatosis of the donor liver on outcome of the transplant (see above) [24, 75].

Serum bilirubin determinations are affected by factors such as hemolysis and nutritional state [57]. Consequently, normal values are reassuring, but increased values can make interpretation difficult. They may reflect primary liver disease (hereditary disorders, cirrhosis, liver ischemia) or hemolysis [46]. The differentiation between conjugated and unconjugated bilirubin may be of some help; however, it does not necessarily distinguish hemolysis (e.g., based on trauma) from hereditary disorders like Gilbert's syndrome and Crigler-Najjar syndrome.

In the process of donor selection, it would seem logical to look for indicators of synthetic capacity of the liver. However, the serum levels of albumin, cholinesterase, and antithrombin III are strongly influenced by the transfusion policy used to stabilize the donor. Fresh-frozen plasma, single donor plasma, and transfused blood all contain these proteins or enzymes and, consequently, will result in false normal or near-normal values. Large volumes of crystalloid infusions in the case of diabetes insipidus will lower the values by dilution and, again, may yield false results. Consequently, routine determinations of the abovementioned parameters in the donor have limited value. Because of the many factors involved, interpretation of the results requires clinical experience and thorough knowledge of possible differential diagnoses. This makes the interpretation of the tests highly subjective and, perhaps, inappropriate in the donor selection process. Based on all of these uncertainties, other tests that may reflect liver viability have been suggested.

Endogenic metabolites reflecting liver function

The ratio between the so-called branched-chain amino acids (valine, leucine, isoleucine) metabolized in muscle tissue and the aromatic amino acids (tyrosine, phenylalanine) metabolized in the liver has been shown to be valid as a indicator of liver function in the dog [68] and in humans [22, 74], including the assessment of the immediate postoperative function of liver grafts [30, 96]. Persson et al., however, reported that the ratio could not discriminate two patients with PNF from ten patients showing an uneventful recovery after liver transplantation [89]. Thus far, no studies have appeared correlating this ratio in the donor with final transplant outcome. Moreover, the practicability of this test is hampered by the time-consuming high-performance liquid chromatography (HPLC) detection technique that is needed. Finally, transfusion of diverse liquids to the donor, such as blood and amino acids containing fluids, will distort the true plasma concentrations of the enzyme levels needed for the ratio determinations, limiting the value of the ratio. These considerations make the amino acids less feasible as a selection parameter.

Bile acid metabolism is an early and sensitive indicator of cholestasis. The commonly used determination technique (enzyme spectrofluorometry) is able to provide data within 2 h. It has been claimed that bile acid clearance may be used as an indicator of allograft function during and after liver transplantation [48, 96, 126]. However, the differential diagnostic potential is limited: serum bile acids have equal or less sensitivity and specificity than routine liver tests [32, 63]. Other disadvantages are that bile acid levels depend on the age of the donor [47, 129] and on nutritional status [31]. Moreover, the clearance of bile acids from the systemic blood is determined principally by liver blood flow, thereby limiting its value as an indicator of parenchymal function [126]. Based on these considerations, introducing it as a selection criterion in the donor situation does not appear feasible, except, perhaps, in the case of neonatal donors.

Another index of liver function that has been studied is the ketone body ratio (KBR), i.e., the ratio between the arterial acetoacetate and β-OH-butyrate levels. This ratio reflects the mitochondrial $NAD^+/NADH$ ratio in the liver and, thus, the energy-producing capacity since the liver is the only organ that makes a net contribution of ketone bodies to the bloodstream [121]. Consequently, this energy-producing capacity of the mitochondria basically determines liver cell viability. It is claimed that the results of KBR analyses can be readily available [125]. The application of KBR in the liver transplant situation has been studied. Osaki et al. found that in a group of 43 patients with 47 transplants, KBR failed to return to normal levels in 3 patients with PNF [82]. In addition, KBR measured in samples taken from the donor immediately before removal of the liver showed a correlation with 1-week graft survival but not with 2-week graft survival, thus indicating that the donor KBR has a correlation with early graft function [84]. It was also shown that high catecholamine administration to the donor reduced the KBR considerably, reflecting a detrimental effect on liver metabolism. However, the KBR did not correlate with blood pressure [137]. Finally, it was shown that KBR measured on the 1st and/or 2nd postoperative day is superior to standard liver function tests in predicting graft prognosis after transplantation [120]. This ratio therefore appears to be promising and clinically usable for prediction of graft outcome.

The lidocaine-MEGX test

The cytochrome P450 enzyme system appears to play a central role in the determination of liver cell viability. In a group of mixed liver diseases, cytochrome P450 activities are significantly impaired compared to normal controls [29, 50]. Also, in humans, the pretransplant hepatic P450 IIIA4 level may have predictive value for short-term liver graft survival [25]. As an additional advantage, P450 IIIA does not seem to be influenced by the age of the subject [98], which should make a test for cytochrome P450 applicable in all age groups.

Formation of the monoethylglycinexylidide (MEGX) metabolite is the first step in the metabolic breakdown of lidocaine via N-deethylation, a reaction that is catalyzed by the cytochrome P450 enzyme system, probably by the P450 IIIA4 subsystem [80, 85]. A great advantage of this MEGX test is that it can easily be performed in the donor situation as fluorescence polarizing immunoassay is available in most hospitals. Results can be obtained within 30–60 min after taking a venous blood sample [78]. In situations of impaired liver function, e.g., cirrhosis, the MEGX formation is reduced and, as a result, MEGX levels are low [80]. The test has been claimed to be a sensitive indicator of transplant outcome, both in adults [79, 108, 109] and in children [39]. In a study of predictive values of donor parameters using a Cox proportional hazards model, Oellerich et al. reported the serum MEGX levels and liver histology to be the only parameters to show a correlation with 120-day graft survival [81]. Adam et al. found significantly lower levels of serum MEGX in discarded livers than in accepted ones [3]. Because the discarded livers were not transplanted, absolute proof of the discriminative value of this test cannot be obtained.

In contrast, several groups have reported on the failure of the MEGX test to predict graft outcome. Livers from donors with a low (< 80 ng/l) MEGX level did as well as livers from donors with levels over 80 ng/l after transplantation [101, 103]. Consequently, doubt still exists about the usefulness of this test. Validation is urgently needed in prospective, randomized, and preferably multicenter trials.

ATP content of the liver: spectroscopy

High-energy phosphates (e.g., ATP) play a central role as a determinant of liver viability [44, 53, 54, 67]. Depletion of ATP stores occurs as a consequence of hypotension, starvation, warm ischemia, and preservation [44, 100]. It is the ATP regeneration capacity of hepatocytes in particular that is considered to play a crucial role in the recuperation of graft function after harvesting and preservation [14, 60]. Thus, theoretically, a technique that would allow assessment of the phosphate composition of the donor liver could play a major role in the selection process. Such a technique could well be magnetic resonance spectroscopy (MRS), which allows assessment of the presence of phosphate compounds in the living cell. Moreover, ^{31}P-MRS also allows one to study tissue pH [18] and the amount of damage to the plasma membrane that defines irreversibly injured ischemic cells [20, 28, 42, 49, 128]. Other features of the technique are ^{1}H-MRS and ^{13}C-MRS, which can, for example, be used to study lactic acid levels [131] and liver glycogen status [112], respectively. An additional advantage is that MRS poses no risk of sterility or temperature changes of a cold-stored organ and is, therefore, a safe, noninvasive technique [132].

With respect to transplantation, MRS has been widely studied in animals, e.g., monitoring of graft function after transplantation [12]. Another animal study showed a strong influence of nutritional status on the ^{31}P-MR liver spectrum [106]. Similar results were seen in the human body too, especially in human hearts [4, 70] and kidneys [15]. In a recent publication, Wolf et al. reported their own experience with MRS on human livers during cold storage. In a series of 25 livers they were able to demonstrate a correlation between relatively high phosphodiester levels (a marker for membrane damage) and insufficient graft function in the immediate postoperative period. A correlation between ATP levels and post-transplant graft function could not be established [135].

Preferably, MRS of the donor liver should be performed before transplantation [124]. There are two possibilities: either to study the liver in situ or to study it ex corpore. There are two main arguments against in situ testing. First, an in situ study of the liver is difficult to perform since the circulating blood and the respiratory movements of the diaphragm cause blurring of the spectra. Second, one must realize that NMR scanners are not widely available yet. Therefore, ideally, the organ should be tested ex corpore in the transplant center after explantation and still be discarded if shown to be nonviable. The prolonged preservation times that have been made possible using the University of Wisconsin preservation solution allow one to follow such a procedure [52]. Indeed, Wolf et al. [135] have shown this method to be quite feasible. Moreover, the method also allows one to monitor viability improvement via so-called metabolic resuscitation [18, 34, 107].

Conclusions

The selection of liver donors will always involve a process of interpretation of available data in less than optimal circumstances. Data will most often be incomplete and additional data difficult to obtain. The selection of liver donors is a process in which several parameters have to be weighed in order to assure a maximum of success. The situation is complicated by the fact, discussed above, that currently used selection parameters, especially those for liver function, have a limited role in the process. We still do not know which donor parameters from the donor history and from the laboratory are essential and which are not. Nor do we know how much each individual parameter contributes within the context of all available parameters. Despite the fact that advances in liver transplantation have increased our knowledge with regard to liver donation, we are still not able to prevent such devastating events as PNF and we probably still discard too many viable donor livers.

Further research is the only means of solving this dilemma. First, research should be aimed at collecting more data on donor condition and at studying the correlation with transplant outcome. Ideally, prospective trials should be undertaken in a multicenter fashion to enable the creation of sufficiently large study groups within a reasonable amount of time. However, a major obstacle is that acceptance of donor livers that are deemed unsuitable for grafting by current criteria is ethically unjustifiable. Thus, allocation bias is created. In addition, one has to realize that transplant outcome is dependent upon recipient condition too. Consequently, studies should correct for this problem, for example, by introducing a system of stratification for recipient condition.

Future research should also be directed towards other parameters, as we may, in fact, presently be looking at the wrong ones. Identification of the determinants of the functional capacity of the donor liver and its tolerance limits to the events occurring in the donor is pivotal. Modern tools, such as MRS and perhaps even positron emission tomography, which enable us to study liver metabolism in vivo, may be helpful instruments in this research. Hopefully, it will lead to the definition of valid selection criteria, criteria that should then be validated in prospective, clinical trials.

In the absence of truly validated selection criteria, the transplant physician should look at the donor as a true clinician would and take the combination of available parameters as they are. They should be weighed against the condition and urgency of the recipient-to-be, and it is the combination of the two that should be considered when deciding whether to accept or to discard a donor liver.

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