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Abstract

Background

In spite of progresses in harvesting techniques, pancreatic graft early failure remains frequent probably due to pancreas microcirculatory system fragility. Present work aim: investigation of the donor’s death cause influence on the pancreas graft.

Methods

A first part was devoted to the morphological investigation of 113 pancreases from <24 hours dead persons divided into groups according to age (8-92 years) and death causes. The pancreas blood vessels were injected with protacryl and submitted to corrosion. Morphometry and histologic examination of the vessels were performed.

In the second part, the functional peculiarities of grafted pancreas from Beating-Heart-Donors were analysed in 43 recipients depending on the donor’s death causes (violent/other).

Results

The anatomic study has confirmed the age influence on the pancreatic vessel physical characteristics. It has also pointed the pancreas microcirculation specific alterations leading to blood extravasations due to brain trauma. In clinics, the temporary influence of a donor’s violent death on the graft quality was probably compensated by adequate management and graft regenerative capacities.

Conclusion

Hydro dynamic shock resulting from severe brain trauma specifically alters the pancreatic microcirculation that represents a potential cause of early pancreatic graft functional worsening. In such occasions, graft angiography before transplantation would be secure.
Does the donor’s death cause have an influence on the morphology and early condition of the pancreas graft?

Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVS</td>
<td>Angle of vessel slope or cone</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CHU</td>
<td>University Hospital Centre</td>
</tr>
<tr>
<td>CIT</td>
<td>Cold ischaemia time</td>
</tr>
<tr>
<td>CKPT</td>
<td>Combined kidney and pancreas transplantation</td>
</tr>
<tr>
<td>CW</td>
<td>Coefficient of winding</td>
</tr>
<tr>
<td>D</td>
<td>Distal</td>
</tr>
<tr>
<td>DBD</td>
<td>Brain death donor/donation after brain death</td>
</tr>
<tr>
<td>DCD</td>
<td>Circulatory or cardiac death donor/donation after circulatory death</td>
</tr>
<tr>
<td>HBD</td>
<td>Heart beating donor</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>K-PTx</td>
<td>Kidney-pancreas transplantation</td>
</tr>
<tr>
<td>LSS</td>
<td>Longitudinal section surface</td>
</tr>
<tr>
<td>M±SD</td>
<td>Mean value ± Standard Deviation</td>
</tr>
<tr>
<td>mm Hg</td>
<td>Millimetre of Mercury column</td>
</tr>
<tr>
<td>NHBD</td>
<td>Non-heart beating donor</td>
</tr>
<tr>
<td>OD</td>
<td>Other causes of death</td>
</tr>
<tr>
<td>P</td>
<td>Proximal</td>
</tr>
<tr>
<td>P-val</td>
<td>Valuable difference</td>
</tr>
<tr>
<td>Tx</td>
<td>Transplantation</td>
</tr>
<tr>
<td>VAC</td>
<td>Venous arterial coefficient</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WIT</td>
<td>Warm ischaemia time</td>
</tr>
</tbody>
</table>

Introduction

The importance of pancreas or combined pancreas-kidney transplantation as a radical treatment of type 1 and type 2 diabetes mellitus and its complications still remains doubtless [1-8]. In spite of tremendous progress obtained in the field of organ transplantation (harvesting, operating techniques, follow-up management [9]), the number of pancreas transplantations (PTx) performed in the world seems to decrease due, maybe, to a kind of confidence decrease in them [6, 11]. In fact, during the last 15-20 years the outcomes of pancreas transplantations have been stabilized around 95% survival at month 1, 80-86% after 1 year, and 72 ± 6% after 5 years [10-18]. That is good, but inferior to the outcomes of heart, lung of liver transplantation [17, 18].

The early complication proportion remains very high (about 58.30% in CKPT [19]) and is a cause or frequent rehospitalization [20], early graft loss requiring retransplantation – 5.2% [21], 7% [22], 35% during a period running from 1978 till 2012-2015 [23].

The main causes of these complications and graft failure pointed by different authors are: surgical damage to the graft during procurement and vascular events mainly thrombosis [24, 25]. Both may be related to the donor condition.

In 2010, Gruessner [14] already pointed at the importance of “careful donor selection” for pancreatic transplantation outcome improvement. Cypel and co-authors [18] supported this opinion.

During the last decade, attention was paid to the influence of the donor’s age, BMI, alcohol use and other factors [25].

A large discussion was opened around the possible benefits or disadvantages of using brain death donors (DBD) or circulation cause death donors (DCD) with rather controversial results: the main conclusion was that DCD was acceptable, though it may be a little worse than DBD, but anyway its use has enlarged the transplantation possibilities [6, 26-29]. Only a few authors have
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observed negative consequences of brain crash or vascular anomaly such as a short portal vein on the PTx issue [23] or blood vessel anatomy [30, 31].

However the blood supply insurance of the graft, hypoxia durations are especially important for the pancreatic graft as far as pancreatic tissue is one of the most vulnerable to ischaemia [25, 32-34].

The anatomy of blood vessels implicated into the pancreas blood supply was well studied by authors of the XX century in general [35-38], in cardiovascular pathology [39] and applied to surgery and transplantation of pancreas [40-46].

Still presently details of harvesting and acceptable hypoxia are the subject of new discussions and proposals.

The insufficient attention to the donor’s conditions before harvesting in NHB donors led to the idea of our investigation consisting of two parts: first - anatomic study on cadavers, dated from the period (1980-87) when it was still possible with local agreement, second – clinical, confronting the conclusions of the first part with early outcomes of pancreas transplantation. Besides the anatomic investigation, it included the study of both age and pathologies of the donors, as far as aging and diseases have interferences that have to be taken into account.

**Methods**

In the first part, a morphological investigation was performed on 113 pancreas from recently (from 4 to 24 hours) dead persons divided into groups according to age and death causes (Table 1).

| Table 1. Cohort subjects depending on death cause and age (according to the current adopted classification of diseases – WHO 1980, and USSR 7th Meeting on Aging Morphology, 1965). |
| | | | | | | |
| Cause of death / age categories | 8-12 years | 16-21 years | 22-35 years | 36-60 years | 61-74 years | 75-90 years | Total |
| Heart & vascular pathology* | 0 | 0 | 5 | 13 | 9 | 11 | 38 |
| Lung pathology | 0 | 0 | 2 | 3 | 1 | 1 | 7 |
| Abdominal organ pathology** | 0 | 1 | 3 | 4 | 1 | 1 | 10 |
| Violent death *** | 3 | 6 | 13 | 19 | 2 | 1 | 44 |
| Oncology | 0 | 0 | 1 | 5 | 7 | 1 | 14 |
| Total | 3 | 7 | 24 | 44 | 20 | 15 | 113 |

* Heart acute and chronic insufficiency (21), stroke (7), thromboses and embolism (3); acquired heart defect (7).

** Liver cirrhosis (1), kidney insufficiency (4), amyloidosis (1), acute inflammatory diseases (5).

*** Acute haemorrhage (5), fall from height (9), transport trauma (6), electro trauma (3), brain trauma (8), asphyxia (11), alcohol poisoning (2).
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For the blood vessel system, an investigation of Protacryl ® injection was performed.

Protacryl is a polymer used in stomatology (granule diameters 0.014-0.07 mm, enlargement coefficient 0.00008).

The solution for injection was prepared and injected under strong unified conditions:

of dilution (1.2 parts of powder for 1 part of standard delivered solvent), that ensured fluidity of the injected mass close to the blood fluidity [47],

of room temperature (20°C),

of pressure (through aorta or truncus coeliac or spleen artery – 100 mm Hg, through portal or spleen vein - 20 mm Hg).

First, the pancreas blood system was washed with physiologic solution at temperature 37°C through cannulas inserted into the corresponding vessels. Solution was delivered by a usual perfusion system, its reservoir placed at 150 cm height from the organ support. Vessels through which the solution flowed out were ligatured. Protacryl injection was provided through a system which ensured smooth filling at a controlled pressure (Fig 1).

Figure 1A. Injection device with pressure and speed control

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Figure 1B. Result of corrosion of the Protacryl injected preparation:

The system was washed with Vaseline oil to ensure a smooth transit of the injected mass. Criterion of complete injection was stabilisation of the pressure registered by manometer and appearance of Protacryl drops at the level of not ligatured peripheral small vessels. The procedure was provided within a container filled with physiologic solution with constant temperature 37°C. Polymerization of the injected mass in these conditions was complete after 15-20 min.

After that, the organ was immerged into concentrated HCl for 24-72 hours, depending of the mass of the injected organ or complex, in a well ventilated place [48]. After that, the object was washed by water flow; then kept in a 1% ammoniac solution during 1 day in order to neutralize remaining acidity, once more washed into flowing water then fixed on a support for investigation. This allowed for the morphometry investigation of arterial and venous compartments. For measuring micrometric instruments (calliper rule or micro meter (precision 0.1 or 0.01mm) and biologic microscope MBS-9 (“LOMO”, Leningrad, USSR) were used.

The following investigations were provided: determination of the form, length, branching peculiarities of macro and micro vessels of the pancreas.

The studied parameters are presented in Table 2.
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### Table 2. Parameters of the anatomic investigation

<table>
<thead>
<tr>
<th>№</th>
<th>Parameter</th>
<th>Measure number</th>
<th>Remarks, measure unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dimensions (Length, width, thickness) of the pancreas</td>
<td>113</td>
<td>mm</td>
</tr>
<tr>
<td>2</td>
<td>Length of the subject</td>
<td>113</td>
<td>cm</td>
</tr>
<tr>
<td>3</td>
<td>Spleen artery inner diameters (proximal /P/, distal /D/)</td>
<td>226</td>
<td>mm</td>
</tr>
<tr>
<td>4</td>
<td>Spleen vein Inner diameters (proximal /P/, distal /D/)</td>
<td>198</td>
<td>mm</td>
</tr>
<tr>
<td>5</td>
<td>Lengths of the spleen artery and vein (real, P-D distance)</td>
<td>212</td>
<td>mm</td>
</tr>
<tr>
<td>6</td>
<td>Winding Coefficient (CW=real length/direct P-D distance)</td>
<td>113*</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Number of first branches of the spleen artery and vein</td>
<td>113*</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Number of anastomoses between spleen vessels branches and branches of inferior pancreatic vessels</td>
<td>67*</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Maximal embranchment of spleen vessels observed</td>
<td>113*</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Surface of spleen vessel longitudinal section (LSS) **</td>
<td>226</td>
<td>artery and vein</td>
</tr>
<tr>
<td>11</td>
<td>Angle of the vessel diameter slope *** (AVS)</td>
<td>226</td>
<td>artery and vein</td>
</tr>
<tr>
<td>12</td>
<td>Venous-arterial coefficient (VAC)****</td>
<td>113</td>
<td></td>
</tr>
</tbody>
</table>

* Number of investigated organs
** Surface of longitudinal section = mean value between proximal diameter (Pd) and distal diameter (Dd) multiplied by the vessel length (L)
*** Cone shape of the vessel = mean value between proximal diameter and distal diameter divided by the vessel length: alpha= arc tg (Pd – Dd):2/L
**** Vein diameter divided by arterial diameter (by Nikonorov AI, 1969 [49])

**NB.** Anastomosis between branches of different vessels of the pancreas were absent in many cases, due to anatomic or pathologic causes. (cf. results).

Microscopic investigation of the pancreas microcirculation was performed by histology methods in 10 subjects in each of 2 groups of potential donors, i.e. after violent death and heart-vessel pathology (age between 19 and 74 years, total 20 persons). Examination of pancreas tissue and the native blood vessel walls (12% formalin fixation, paraffin embedding, haematoxylin eosin, azure eosin, fuchsine and Van Gieson staining, slices 5-10 mcm thickness).

For Statistics, computerized programs M-3040 in the informatics laboratory of the People Friendship University named after P. Lumumba were used. The following methods and calculation: Mean value, standard error, correlation, two-dimensional dispersion diagram which allowed elimination of excessive values, liability of results evaluated by methods of parametric statistics (Student coefficient) and not parametric statistics (X²).

The second part of the study was devoted to analysis of pancreas harvesting and 43 transplantations performed in 21 males and 22 females aged 29±12 years, BMI 24±8, at CHU Erasme (Free Brussels University) during the last 12 years taking into account the causes of the donor’s death: violent (8 males/8 females), or other ones (13 males/14 females).
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The donor allocation was only national due to the limited time of ischaemia required (since 2010 only one donor has been accepted from Luxemburg). The proposition of the pancreas graft was accepted depending on active recipients.

For harvesting, in all the cases, the graft was isolated after brain death was declared and the conserving solution perfusion was immediately started and the heart beating stopped.

The pancreas was transplanted into the right iliac fossa. The exocrine output was ensured by a bladder anastomosis (15 early grafts) or by a digestive anastomosis (28 last ones).

The cold ischaemia time has been registered from the moment of the donor’s aorta clamping till the pancreas graft was removed from the cold storage bag and the vascular anastomosis had been started. It never exceeded 15 hours. Warm ischaemia time indicates the time necessary for vascular suturing.

In 19 out of the 43 pancreas, UW solution was used during procurement, versus HTK in 9 donors.

All full organ pancreas procurements were accompanied by multi organ procurement procedure (when the donor was in good condition following the guide lines of “Eurotransplant”). The main factors considered for pancreas graft acceptance were: age, BMI, stay in IU, liver and pancreas function of the donor. The contra indications were: age > 45 years, liver and pancreas dysfunction, long reanimation or cardiac arrest of the donor, drugs intoxication, radiological or macroscopic signs of the pancreas oedema or haemorrhage.

The studied parameters concerned both donor management and global evaluation of the graft condition. The characteristics of the donor management considered were: Donor stay in ICU, Reanimation or not, duration of cold and warm ischaemia (including the surgical procurement of the organ and time between heart beating stop and isolation of the pancreas), injection or not of catecholamine and volume expander.

For graft condition and function evaluation, during the first 5 post-operation days, measure of blood C-peptide, measure of amylase and lipase contents in abdominal drainage fluid and in blood, were used. These measures were realized by Roch Modular P800 Analyser system till 2015 and later by Roch COBAS 8000 Analyzer in the laboratory of the ERASME Hospital of the Free Brussels University.

The following values were considered as normal: for blood glucose 70-100 mg/dl, for blood C-peptide - 0.57 - 1.47 mille mole/l, for serum lipase - < 75 U/l, for serum amylase - < 125 U/L.

Results

First part.

The following factors were considered as the most important influencing the organ blood flow characteristic: 1. coefficient of winding (CW, resulting from length modifications), 2. longitudinal section surface (LSS) 3. vessel cone angle (VCA), resulting from diameter modification), 4. embranchment and 5. anastomosis development, as influencing irrigation of the parenchyma. But diameters, length and shape of the splenic vessels were also considered.
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As far as the group of 8-16 years of age was weakly represented (3 persons) and except the diameters and length of the splenic vessels, the other indices did not significantly differ of those measured in the 17-21 year group, the data from children were not always presented here.

In the evaluation of the influence of aging on the pancreas irrigation, the measures of the spleen vessels have shown that during life, the dimensional characteristics of both the arterial and venous system of the pancreas significantly evolved (Fig. 2).

**Figure 2.** Evolution of studied parameters of the splenic vessels depending on age group. (Abscissa: age category: 1 -8-12 years, 2- 16-21; 22-35; 36-60; 61-74; 75-90 years). A. Diameters, B. Length (cm, M+/SD), C. Form (right, arch, sinuous, spiral), D. Winding coefficient (angle grades), E. Longitudinal section surface (mm²).
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C.

Age influence on the splenic artery shape (%)

D.

Age influence on the winking coefficient of the splenic artery (red) and vein (grey)

E.

Age influence on the longitudinal section surface of the splenic artery (red) and vein (grey)
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As Figure 2 shows, proximal and distal diameters of artery were increasing but stabilized after 61 years (Fig. 2A) and the length of both spleen artery and vein increased all through life (Fig. 2B). An arc-shaped, sinuous and spiral form of vessels (mainly artery) has appeared in the group 35-60 years and further its frequency increased (Fig. 2C). This explains the increasing winking coefficient especially in artery (Fig. 2D). Arc tg of the angle of the arterial cone (AVS) decreased with aging, the vein one – increased, which signifies that artery distal segment becomes relatively narrower and vein one – larger in elderly persons in comparison with young people. Calculation of longitudinal section surface also shows an increase of the values with time. This may condition a decrease of the pancreas blood irrigation due to aging.

Vein- Arteria- coefficient (VAC) evolution was a bit different in the head and the tail of the pancreas with aging (Table 3).

Embranchment of the spleen artery did not show any trend for increase with aging neither in quantity of branches, nor in degree of embranchment: mean values remained the same for arteries, showed a little increase for the veins (Table 3).

**Table 3.** Evolution of the vein-artery coefficient, embranchment (number of vessels directly coming from artery or reaching vein) and intra organ anastomoses (in % of the initial value in young persons) with aging (M+/SD)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N</th>
<th>VAC in the head / VAC in the tail</th>
<th>Embranchment artery / vein</th>
<th>Intra organ anastomoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-21</td>
<td>7</td>
<td>2.08±0.71 / 2.41±0.59</td>
<td>5.3±2.89 / 14.0±3.46</td>
<td>100%</td>
</tr>
<tr>
<td>22-35</td>
<td>24</td>
<td>2.32±0.54 / 2.38±0.74</td>
<td>5±0.895 / 13.4±2.7</td>
<td>90.2</td>
</tr>
<tr>
<td>36-60</td>
<td>44</td>
<td>2.33±0.84 / 2.18±0.46</td>
<td>4.9±1.64 / 16.9±4.21</td>
<td>82.6</td>
</tr>
<tr>
<td>61-74</td>
<td>20</td>
<td>2.09±0.37 / 1.85±0.33</td>
<td>5.2±2.15 / 15.7±3.11</td>
<td>82.5</td>
</tr>
<tr>
<td>78-90</td>
<td>15</td>
<td>2.42±0.51 / 1.76±0.77</td>
<td>5.1±2.26 / 17.7±3.8</td>
<td>80.0</td>
</tr>
</tbody>
</table>

Development of intra organ anastomosis was noted in all the subjects aged till 21 years, so it is taken as 100%. In the group 22-35 years, development of anastomosis decreased till 90.9% and the tendency continued in the older groups.

The influence of sex and body height on all studied dimensions was not significant, except on the quantity of direct arterial branches and surface of the artery longitudinal section which are less important in women who are smaller in size than men.
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The influence of the donor’s pathology causing the death on the blood vessels morphology.

Though oncology, abdominal acute or chronic events and severe lung pathology are contraindications for transplantation, this kind of patients was considered for comparison and determination of the pathology influence specificity of observed vascular alterations. The results are presented in Figure 3 and Table 4.

Figure 3. Comparative influence of different causes of death on the main properties of splenic vessels. A. Form, B. Diameters, C. Length, D.CW, E.LSS,

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Table 4. Evolution of the vein-artery coefficient, embranchment and intra organ anastomoses depending on donors’ pathology (M+/SD)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>N</th>
<th>VAC in the head</th>
<th>VAC in the tail</th>
<th>Embranchment artery</th>
<th>Embranchment vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Violent death</td>
<td>22</td>
<td>2.23±0.52</td>
<td>2.2±0.54</td>
<td>5.4±1.89</td>
<td>15.3±3.8</td>
</tr>
<tr>
<td>Vascular &amp; Heart</td>
<td>18</td>
<td>2.07±0.47</td>
<td>1.95±0.43</td>
<td>6.4±2.52</td>
<td>17.0±3.7</td>
</tr>
<tr>
<td>Oncology</td>
<td>8</td>
<td>2.57±0.75</td>
<td>2.3±0.54</td>
<td>4.4±2.3</td>
<td>17.3±5.1</td>
</tr>
<tr>
<td>Lung</td>
<td>6</td>
<td>2.0±0.36</td>
<td>1.57±0.64</td>
<td>4.8±1.5</td>
<td>16.3±6.0</td>
</tr>
<tr>
<td>Abdominal</td>
<td>8</td>
<td>2.27±0.049</td>
<td>2.78±0.53</td>
<td>5.4±1.9</td>
<td>15.8±3.4</td>
</tr>
</tbody>
</table>
Does the donor’s death cause have an influence on the morphology and early condition of the pancreas graft?

In the case of violent death, macroscopic morphological parameters did not significantly differ from those observed in general in young people: low winding coefficient (1.24+/-.024), high AVS, high embranchment up to 6 and high surface of longitudinal section. VAC was 2.23+/-.0.52 and in the head 2.2+/-.0.54. Nevertheless, Protacryl extravasation was regularly observed at every level of embranchment after transport trauma and fall from high punts (Fig 4 A). Microscopy in these cases has shown alteration of muscle layer of arteries and veins, under endothelial oedema and fragmentation of collagen at all the levels. Elastic layer was well conserved (Fig. 4 B, C). In the parenchyma of the gland, necrosis, apoptosis, oedema between cells were also observed (as a result of warm ischaemia, vascular alterations or both?).

**Figure 4.** Peculiarities of the influence of violent death on some studied parameters.

A. Extravasations (arrow) at the level of 3-4 embranchment of splenic artery,
B. dislocation and fragmentation of collagen fibres in arterioles, C. sub endothelial and cellular oedema, apoptosis of endothelial cells in arterioles, small veins and capillaries.

In heart and vascular pathology sinuous vessels were observed in 70.3% of the cases, spiral shaped form – in 6.1%. Right shape was registered only in 18.9%. Coefficient of winding (CW) reached 1.47+/-.0.13. VAC Embranchment was well developed (4.3+/-.0.2). Microscopy has mainly shown extra cellular oedema with dissociation of the islet cells elements. The structure and morphology of the vessel walls were conserved.

In lung pathology, the main shape of the vessels was the sinuous one (66.7%), the surface of longitudinal section was high (404,6+/-.103.5 mm²), the proximal diameter of the spleen artery was very high (5.2+/-.0.4mm). VAC was significantly diminished in the tail part of the pancreas, AVS was practically doubled (2.8+/-.0.5 versus 1.0 to 1.4 in other pathologies).

In abdominal pathology, the diameter of all the vessels was increased (hyperaemia due to inflammation), winding coefficient too, VAC was significantly increased in the tail (2.78+/-.0.53). AVS was low (1.34+/-.0.08).

In oncology, the most characteristic feature was an increased vessel diameter, VAC of the pancreas head (2.57+/-.74), AVS, and vein LSS.
Second part

The analysis of obtained data has shown that the conditions of management of the donor and the graft – duration of ICU stay, frequency of reanimation manipulations, arterial systolic and diastolic pressure were similar in both groups, as well as duration of the cold and warm ischaemia conditions. Nevertheless, the necessity to use volume expanders and catecholamine for the donor stabilization in the cases of violent death was significantly higher than in other death causes (Table 5).

Table 5. Characteristics of the donor and graft management. (M±SD)

<table>
<thead>
<tr>
<th>Indices</th>
<th>Violent death</th>
<th>Other causes</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reanimation (Yes %)*</td>
<td>23</td>
<td>30</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>ICU stay (hours)</td>
<td>25.6±12</td>
<td>33.9±35</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Arterial blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- systolic</td>
<td>118.2±17.3</td>
<td>113.0±39.0</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>- diastolic</td>
<td>64.6±12.0</td>
<td>68.16±24.66</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Catecholamine use (Yes - %)</td>
<td>87.5</td>
<td>62.5</td>
<td></td>
<td>s</td>
</tr>
<tr>
<td>Volume expansion (Yes %)</td>
<td>62.5</td>
<td>44.4</td>
<td></td>
<td>s</td>
</tr>
<tr>
<td>Cold ischaemia time (hours)</td>
<td>13±3</td>
<td>11.28±2.76</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Warm ischaemia time (minutes)</td>
<td>38.25±2.98</td>
<td>36.06±10.03</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Total patients</td>
<td>16</td>
<td>27</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

* In the series “other” in 7 cases the performance of reanimation or not was not mentioned so the cases were excluded and N total was 36

As to functional features of the grafts, the results of their measure not only in blood but in the abdominal drainage liquid are presented in Table 6.

Table 6. Functional characteristics of the graft depending on the cause of the donor’s death (M±SD)

<table>
<thead>
<tr>
<th>Indices</th>
<th>Violent death</th>
<th>Other death causes</th>
<th>Normal values</th>
<th>p *VD/OD **day 0/day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>C peptide</td>
<td>6.64±5.34</td>
<td>5.66±3.3</td>
<td>0.57-1.47 mM/L</td>
<td>ns</td>
</tr>
<tr>
<td>Drainage Lipase</td>
<td>8280±1719.2</td>
<td>6423±1495</td>
<td></td>
<td>ns *</td>
</tr>
<tr>
<td>- day 0 min - max</td>
<td>352-511930</td>
<td>359-45208</td>
<td></td>
<td>** &lt;0.05</td>
</tr>
<tr>
<td>- day 5 min - max</td>
<td>2571±5266</td>
<td>1188±3975</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Test</th>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 2</th>
<th>Day 5</th>
<th>Day 2</th>
<th>Day 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drainage amylase</td>
<td>3059.6±4047</td>
<td>1343±2410</td>
<td>226.7±400</td>
<td>90.1±86</td>
<td>183±187</td>
<td>77.8±70</td>
<td>16</td>
</tr>
<tr>
<td>min - max</td>
<td>358-12500</td>
<td>52-7282</td>
<td>1121.8±450</td>
<td>131-4152</td>
<td>176.5±111.3</td>
<td>153.2±70</td>
<td>27</td>
</tr>
<tr>
<td>Blood lipase</td>
<td>2699.9±4865</td>
<td>2548,8±1440</td>
<td>184.9±191</td>
<td>98.3±59.6</td>
<td>195.1±145</td>
<td>195.5±145</td>
<td>16</td>
</tr>
<tr>
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<td>2548,8±1440</td>
<td>153-4152</td>
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</tbody>
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As shown in Table 6, the mean values of the considered indices were higher in VD series at day 0. But the SD was enormous, because of some extremal cases especially in VD series and thus no significant difference could be observed between the functional results of TxPa in both series at any moment. The tendencies of normalization of excretory function were evident except for blood lipase and drainage amylase in OD series.

**Discussion**

First of all, it is necessary to point the limits of the methods used, especially in part 1 of the study.

In part I, as far as the material was constituted of cadavers examined through 6-24 hours after death, it is possible to incriminate post mortem natural changes as the cause of observed alteration. But this may concern only parenchyma of the gland and not the anatomic specificities of the macro vessels, as confirmed by comparative histologic studies. We may also compare these ischaemia delays with the duration of warm and cold ischaemia in clinic procurement and find that they are comparable on many points.

Another limit is the absence of standard control of healthy people and living patients with pathologies mentioned in this study. This could be envisaged by performing angiographic study on volunteers or using existing angiographic observations performed in standard controlled conditions. But presently how such a demand will be considered by Ethic Committees?
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It is also necessary to take into account that mutual influence of age and pathology are not excluded: cardio-vascular diseases are more frequent in elderly persons and may accentuate the influence of aging.

At least we could not study the microcirculation of the potential grafts by injection and corrosion method in clinics. But blood vessels microscopy including capillaries histologic examination has confirmed and explained the alterations noted at the macroscopic level.

In part II, the delayed observations are missing and the difference between measured values is extreme so that the increase of the patients’ number could not introduce real changes. The early results may confirm the absence of significant difference between the issues of the two grafts groups.

That is probably due to an adequate management during harvesting and after transplantation. It would be interesting to track morphologic (early fibrosis) and consecutive functional weakness due to microcirculatory defects in the violent death group grafts.

Nevertheless, some facts could be pointed at.

Our anatomic investigations on cadavers have clearly shown the following.

Considering the influence of age on the pancreatic vessel configuration, comparative studies have shown that relatively to the groups 8-12 years and 22-35 years the spleen artery and vein length began to differ significantly (p = 0.01 or < 0.01) in the groups from 36 years to 90 years. The most affected is the arterial system.

The diameters in proximal and distal parts of the splenic artery significantly differ from the group 8-12 years beginning from 17-21 years, whereas between the different age groups from 22 – 35 years till 90 years a significant difference can be found no more.

The spleen artery length increases all through the life: at the beginning in relation with the natural growth; later, after 35 years, probably due to the increase of the wall rigidity, that causes an increasing winding mainly of the artery, and flow alterations. The surface of longitudinal section of the artery begins to differ significantly from the values observed in the 22-35 year group, and after 36 years – especially after 61 years, no significant difference between different age group in the arterial embanchment.

The same global trends were observed with the splenic vein. They also concerned the length, the form and the diameter and as a consequence, the winking coefficient and the longitudinal section surface, but these modifications were some different less important than arterial ones and did not concern embranchment.

It is to be noted that a significant diminishing of the intra organ vascular anastomoses was observed after 40 years, which reached 18.2-20% after 61 years.

So the cut age for the majority of vascular morphologic alterations start seems to be 35 years that corresponds to literature data [31 and others], though for some authors it may be 45 years [15]. More aged persons could have a well conserved pancreatic blood system and, on the contrary young people could have mostly altered pancreatic vessels (see dispersion curves) and anomalies such as short portal vein [30, 41].
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Considering the impact of the donor’s death cause may have on the graft quality, our data have shown that different pathologies could cause different alterations. The specificity of these changes and alterations was observed and statistically confirmed (see correlation links, Table 4). Our observations have given a complementary justification of refusal for lung, abdominal and oncologic patients (as well as too old patients). Unexpectedly, violent death, especially accompanied by serious brain trauma (fall from height, transport trauma) may cause serious alterations of the vessel walls (sub endothelium oedema, collagen fibres dislocation) which lead to extravasations observed at the level of 3-4 embranchment, a decreased diameter and length of the splenic artery and a diminished number of anastomoses between pancreas and spleen vessels. These vascular serious alterations evoking a vascular spasm, are probably due to hydraulic/hydrodynamic shock occurring at the moment of the contact of the head with hard object. The observed microcirculation injuries may increase thrombosis risk after grafting. Some authors have pointed bad results with certain DBD donors [23, 26, 29, and 55], that confirm our cautiousness with that kind of donors.

In these conditions, a preliminary investigations of potential pancreas graft blood system may be important for evaluation of the organ vascularisation. This explains other authors proposal of pre-procurement tests including preventive angiography, resonance imaging and other, destined to verify the graft quality and hence to improve the outcomes of PTx [31, 51], especially in the case of not heart beating donor and Tx of the distal segments of the pancreas (that is already performed in living donors [29, 33, 54].

Interestingly, the peculiarities of female spleen vessel characteristics should allow organ donation of females being more secure in groups older than 36 years verifer.

Clinical investigations have shown that the donors after violent brain death need more volume expansion than other ones, more catecholamine injection but it was possible to maintain an adequate arterial blood pressure which significantly does not differ. The other conditions of managing donor or graft were statistically the same in the two groups.

Nevertheless, a tendency to worse functional value of the transplants harvested after violent death is to be mentioned at day 0 post transplantation.

Later, the results were close to each other. Isolated cases of high values of blood lipase or amylase corresponded to the rare cases where complications were recorded at the first day. Drain amylase and lipase were more significant at the day 0 the results were significantly high in the group VD, but normalization was practically as complete as in the OD group within 5 days. It means that on one hand the graft condition was poorer soon after transplantation probably because of the microvascular lesions of the pancreas, on the other hand the last is supposed soon to recover. Hence, the VD may be the cause of some functional and morphologic troubles of the pancreatic graft, but in clinics, management during and post harvesting, post operation follow-up seem to stir the differences (if they are expressed) and do not affect the fate of the recipient at day 5 post Tx.

Finally, as some authors have observed, transplants of different origins can be successfully used: there are some differences between DBD and DCD donors [55], there is an evolution in the quality of donors [56] but the calculation of PCRI is of small usefulness [57]. Presently, the only factors that may influence the issue of pancreas transplantation are ischaemia duration and age.
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of the donor. As our observations have shown, there are not only the age of the organism but also the rising frequency and severity of pathologies which affect elderly people.

As for ischaemia, pancreas tissue and microcirculation are known to be especially sensible to it. In our cases, WIT average was about 40 min. It may be due to the fact that, even in heart beating donors, harvesting begins by the heart and lungs that stops the blood circulation of other potential grafts, and ends with pancreas isolation after 30-45 min. If the sequence of one or the other organ transplantation in CKPTx seems to have no importance [19, 26,] in harvesting the situation may be different because of the supplementary ischaemia and thrombotic risk increasing. Would it not be wiser to inverse the sequence of harvesting: first digestive organs, then lungs and heart, so that oxygen and blood providing would be ensured to the very moment of each organ isolation?

The complexity of pancreas transplant viability reminds scientists and clinicists that there are other perspectives and alternatives to PTx – bioengineering and islets auto transplantation, when it is possible [58-60].

Conclusion

1. Our anatomic study confirms and justifies the main existing criteria of potential pancreas graft harvesting.

2. Some usually ignored causes of possible worsening of the results of pancreas transplantation are reviewed, such as: pancreas microcirculation injuries due to hydraulic shock in violent death, and artificial increasing of the ischaemia delay during harvesting.

3. Two propositions come from this study: imaging of the pancreas potential graft blood system at the moment of harvesting, in cases of doubt about the integrity of its vascular system; as well as inversion of the harvesting schedule beginning with abdominal organ isolation while lung and heart still ensure blood and oxygen supply, and ending with heart and lung collection.

Acknowledgements

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References


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