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Screening and assessment of the donor heart

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Abstract

Why screening?

Thirty years ago most donors suffered from head trauma (“Morbus Kawasaki”) and a donor older than 35 years was beyond the pale, i.e. donors were young and healthy, and since these early days of transplantation donor hearts have been regarded as healthy “per definitionem” (1). However, due to the general organ shortage the criteria for the acceptance of donor hearts have been widely liberalized. According to the current quarterly data report of the International Society for Heart and Lung Transplantation (ISHLT) nearly two thirds of donors in Europe (64.3%) were older than 35 years, more than a quarter (26.0%) were even older than 50 years and less than 10% of organ donors suffered from head trauma (2). Meanwhile the average (European) donor is 45 years old and is suffering from intracranial bleeding, i.e. the so-called “donor pool” represents a subpopulation with significantly elevated risk for cardiac diseases such as coronary atherosclerosis and hypertension-related myocardial hypertrophy (Fig. 1). Unfortunately, daily experience shows that donor heart screening has not been adapted to this development (3). Therefore, the question “Why screening?” is not as trivial as it may look: Donor coronary angiography is still an exception (performed in 5-10% of donors) despite the fact that [1] the prevalence of significant atherosclerotic coronary artery disease (CAD) in the donor pool is about 20%, [2] the risk of CAD transmission without angiography is about 5% to 10% despite organ inspection by the harvesting surgeon and [3] the risk for early graft failure with transmitted significant CAD is three times as high (4,5).

Key words: organ donor, heart donor, donor management, screening, coronary angiography, organ transplantation, heart transplantation

General aspects

The real goal of donor heart assessment is not to estimate the functional status of the heart just before the organ harvesting but rather to predict the performance of the transplanted graft after weaning from the extracorporeal circulation and in the postoperative period. For that, hemodynamic and myocardial assessment during organ harvesting

is important but is only one of several aspects. One also has to take into account the cumulative injury by “preexisting damage” of the donor heart and “brain-death-related stress” (6). This cumulative damage/stress may still be functionally inert but become evident after subsequent damage by ischemic time and reperfusion (7, 8).

Moreover, “donor-independent” parameters, e.g. length of ischemic time, size match-

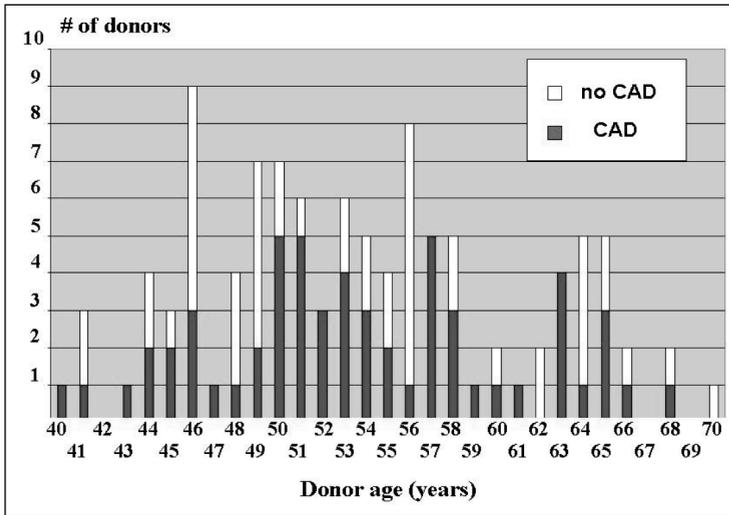


Figure 1: Prevalence of atherosclerotic lesions visible in 107 consecutive heart donors older than 40 years was 53.3% (57/107). [Unpublished angiographic data from study of reference 3]

ing between donor and recipient as well as the pulmonary vascular resistance (PVR) of the recipient (9), have to be considered, since these parameters represent the hurdle that has to be cleared by the cumulatively damaged graft.

In this sense donor assessment means “integrating” all these given parameters to answer the question of whether the donor graft, under all the given conditions and circumstances, will be suitable for the intended recipient.

Pre-existing damage

The most common cardiovascular diseases in the industrial countries are (coronary) artery disease and hypertension, leading to myocardial hypertrophy.

Angiography (coronary atherosclerosis)

As shown by pathological studies, in our cultural area asymptomatic coronary atherosclerosis is common even in children and young people (10, 11). The prevalence of significant coronary atherosclerosis – defined as a 50% stenosis of at least one main coronary artery

– is found in about 20% (including 3% coronary occlusions) in a “healthy” population with a mean age of 20 to 25 years (10-13). Therefore, coronary angiography, at least in donors older than 40 years or according to the anamnesis and/or risk factors – is a “sine qua non” for the adequate management of this issue (4).

Up until now there is no evidence which kind or degree of transmitted coronary atherosclerosis really impairs the post-transplant outcome since – as mentioned above – angiography in donors younger than 60 years has been regarded as unnecessary. On the other hand, although there are individual patients with excellent long-term outcome despite significant and (postoperatively) well-documented transmitted coronary atherosclerosis, probably many of those transplantations end in so-called “early graft failure” (5). Of course, recent infarction and diffuse coronary sclerosis are contraindications without any doubt, but a single stenosis with good performance of the dependent myocardial area seems to be acceptable (5), especially if it is treated interventionally during donor angiography or by concomitant bypass surgery during transplantation (14,15).

Echocardiography (myocardial hypertrophy)

There is no doubt that myocardial hypertrophy represents a risk factor concerning post-transplant outcome. However, at the moment it is unfortunately not known what degree of myocardial hypertrophy impairs the outcome and to what extent, since documentation of echocardiographic donor findings incomplete. A refined protocol for donor echocardiography has to be recommended, that includes the degree of myocardial hypertrophy as well as wall motion abnormalities, valvular dysfunction and anatomical/congenital disorders (Table 1). However, such a comprehensive standard donor echo protocol has not yet been introduced and, therefore, at present only the "prevailing expert opinion" is available, which is that a heart with a septum thicker than 12 mm represents an elevated risk and that an organ with septum thicker than 16 mm should be declined (16).

Furthermore, persisting wall motion abnormalities (see below), a left ventricular end-diastolic diameter of >55 mm, a valvular stenosis (of any degree) and valvular incompetence of more than first degree represent an elevated risk. First degree valvular incompetence and an atrial septal defect have no impact concerning transplant outcome.

Age

Finally, it has been calculated by data analysis of the Cardiac Transplant Research Database (CTR) that (myocardial) age is a further and independent risk factor (17). Young et al. showed that the extent of negative impact of risk factors (need for inotropic support, ischemic time etc.) is aggravated by donor age and they depicted these correlations in risk diagrams (17).

Brain death induced damage

The impact of brain death on myocardial performance has been described in detail by Szabo (6). Therefore, only specific aspects of donor graft assessment will be mentioned here:

Echocardiography allows reliable assessment of cardiac valve function and myocardial hypertrophy as well as the verification/exclusion of congenital malformations. However, the assessment of myocardial performance is problematic since global and even regional ventricular dysfunction may be brain death induced and these wall motion abnormalities may be reversible within hours; after optimized donor management and recovery these marginal organs can be transplanted with excellent results (18). Therefore, serial echocardiography is required before a graft is rejected because of myocardial dysfunction (18, 19).

In experimental studies acute brain death is followed by a short phase of intense vagal activity with bradycardia and hypertension and by a second hyperdynamic phase, the so-called catecholamine storm (20-23). Adrenaline and noradrenaline levels rise more than 100-fold and systolic arterial pressure rises up to 400 mmHg; however, due to an extreme increase in total peripheral resistance (TPR) cardiac output decreases, in some cases down to a short-term circulatory arrest (24). Subendocardial ischemia and necrosis occur accompanied by ST-elevation, Q-waves, multifocal ventricular ectopic beats and runs of ventricular tachycardia in ECG as well as transient ischemic mitral valve incompetence with an increase of left atrial pressure (LAP) up to 90 mmHg (24). These circumstances are regarded as responsible for the reversible wall motion abnormalities mentioned above. These two early phases of brain death are followed by a third and relatively stable phase: a steady deterioration of the donors' peripheral circulation occurs, due to endocrine and metabolic changes. Despite optimal therapy including ventilation, restoration of hormones and blood vol-

Table 1: Parameter list for assessment of donor hearts

	Risk normal	Risk increased	Risk considerably increased	Validity
Donor age	<50 years	50 - 65 years	>65 years	evidence
Ischemic time	<240 min.	>240 min.		evidence
Circulation parameter				
Dobutamine/dopamine	<6µg/kg BW	6-10µg/kg BW	>10µg/kg BW	evidence
Adrenaline/noradrenaline	0	>0		evidence
Mean arterial pressure	> 60 mmHg	50-60 mmHg	< 50 mmHg	experts
CVP / LAP (PEEP 5)	<10 / <12	10-15 / 12-15	>15 / >15	experts
Central/mixed-venous saturation	>75%	50-75%	>50%	experts
ECG				
Infarct (QRS)	no		yes	experts
ST-segment	no / yes			evidence
Bundle branch bloc		X		experts
chron. AF		X		experts
VES	single	unifocal	multifocal	experts
Sokolow index		>3.5		experts
Echocardiography				
Ventricular septum	<12 mm	12-16 mm	>16 mm	experts
LVEDD	£55 mm			
>55 mm		experts		
Shortening fraction	>30%	20-30%	<20%	evidence
Regional hypokinesia	no	yes	yes	evidence
Valve stenosis	no	yes		experts
Valve insufficiency	1st degree	≥ 2nd degree		experts
Atrial septal defect	no / yes			experts
Coronary angiogram	no lesion	single lesion	diffuse sclerosis	questionable
Chemistry				
Troponin T	normal	elevated	elevated	evidence
Procalcitonin	normal	elevated	elevated	evidence
Serum-Na ⁺	130-160 mmol/l	>160 mmol/l		experts
Hemoglobin		<7 g/dl		experts
pH (normal PaCO ₂)		<7.2		questionable
Resuscitation		at time of brain death/injury	during later course under optimal donor management	experts

ume, correction of electrolytes and acid base balance, the vascular bed becomes refractory to vasoconstrictory support (25).

In the clinical setting the intensity of the catecholamine tide ("catecholamine storm") depends, among other factors, on the mode of brain death (20). Therefore, the brain death induced injury of the donor organs varies over a wide range. However, the assessment of the donor heart takes place during the third phase of brain death, i.e. several hours after the catecholamine tide has faded away. Since the brain death induced injury may be functionally inert – but may become relevant after subsequent damage by ischemic cold storage and reperfusion – it is recommended not only to assess the heart by ECG, echocardiography and hemodynamics but also to gain an idea of the troubles that the heart may have had to overcome already, e.g. by measuring troponin T as a marker of myocyte injury (26). In this context it should be mentioned, that brain death is also associated with an inflammatory response that primes the endothelium for cumulative injury during the subsequent stages of ischemic cold storage and reperfusion. Therefore, procalcitonin as a marker of inflammation – and as an indirect marker of intensity of brain death induced injury – has been found to be a parameter of prognostic value (27).

Hemodynamic and myocardial assessment

For the hemodynamic assessment as well as for the appropriate management of the donor with regard to the pathophysiology of brain death, mean arterial pressure (MAP), preload and afterload (CVP, PCW/LAP, PAP, TPR), cardiac output and/or mixed-venous oxygen saturation, i.e. from arterial and venous lines as well as a pulmonary artery catheter, are required (16). Mainly, the hemodynamic assessment has to differentiate between the three most common cardiovascular problems of the third phase after brain

death mentioned above: 1) hypovolemia due to diabetes insipidus because of brain death related hypophyseal insufficiency 2) brain death related peripheral vasoplegia and 3) myocardial insufficiency as a result of combined pre-existing and brain death induced damage.

Hypovolemia will be assessed by measuring the central venous pressure (CVP) considering the ventilation pressures (PEEP) and by the swing of the arterial pressure curve. Right heart filling can be assessed by transesophageal echo (TEE) or by direct inspection after opening the pericardium.

Brain death related peripheral vasoplegia (TPR less than $800 \text{ dyn} \times \text{sec} \times \text{cm}^{-5}$) may require perfusor therapy with low doses of nor-epinephrine; however, doses higher than 0.1 mcg/kg/min are suspected to obscure a need for inotropic support via β -adrenoreceptors, due to myocardial dysfunction.

As shown by an analysis in 1719 consecutive primary heart transplantations performed at 27 institutions, donor hearts requiring inotropic support of up to $6 \mu\text{g/kg/min}$ of dobutamine or dopamine can be accepted as so-called "marginal grafts" with acceptable outcome (17).

NOTE: An excessively elevated serum sodium ($\text{Na}^+ > 160 \text{ mmol/l}$) results from inadequate management of diabetes insipidus, i.e. inadequate donor management, and therefore should be an alarm signal regarding all other aspects of donor management.

"Donor-independent" parameters

According to data analyses of the ISHLT Registry and the CTR Database some "donor-independent" parameters have a great impact on the outcome after transplantation and should be taken into account:

Ischemic time

The impact of ischemic time and reperfusion is described in detail by Wagner (7). Therefore, at this point only some logistic aspects will be mentioned since ischemic time depends on many more parameters than is apparent at first glance: (1) Experience of the harvesting surgeon [the time from aortic clamping to storage in the ice box including back table preparation may vary between 15 min. and 45 min.] as well as experience of the implanting surgeon and/or recipient situs [duration of implantation may vary between 30 min. and 60 min. or even longer if difficult preparation or complex reconstruction is required]; (2) Distance between donor hospital and transplant center and transport conditions [depending on vehicle type and traffic conditions (rush hour or road construction sites) time for ground transport may differ by 30 min. and more and (especially propeller driven) aircraft may need much more time on the way back in the case of headwind]; (3) Logistic experience of the transplant team and coordinator.

Donor-recipient matching

A donor who is more than 10% smaller (height may be more valuable than weight) than the recipient carries an independent risk factor, especially if the donor is female and the recipient male (24).

The impact of pulmonary vascular resistance (PVR) is described in detail by Wagner (9). In general, a PVR of the recipient of less than 4 Wood units and a transpulmonary gradient of less than 12 mmHg are acceptable; however, the relation between risk and PVR is logarithmical (28). It should be mentioned that PVR is, at least in part, reversible by drugs or NO ventilation in most patients but this should already be tested at the time of recipient listing and the test should be repeated every 6 months.

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