ORIGINAL ARTICLE

Can Heart Donation Exclusion Factors Be Overcome?

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Introduction and objectives. A shortage of heart donors is limiting the expansion of transplant programs. Our aims were to investigate the impact of different heart donation exclusion factors and to examine ways of increasing the donor pool.

Patients and methods. We carried out a retrospective descriptive study of individuals donating organs at a university hospital over a ten-year period. Males under 50 years of age and females under 55 years were regarded as potential heart donors. We recorded the etiology of brain death, initial heart donation exclusion factors, and later reasons for rejection.

Results. We studied 130 organ donors, 69 of whom were regarded as potential heart donors. Thirty-nine actually became heart donors (i.e., 30% of all donors and 56.5% of those of a suitable age). Thirteen were excluded because of a history of heart disease; the majority died from ischemic or hemorrhagic stroke, excluding rupture of an aneurysm or arteriovenous malformation (P<.005). Another 11 donors were excluded because of ventricular dysfunction, which was probably secondary to brain death in 10 patients. Ventricular dysfunction accounted for 30% of cases of heart donation exclusion. A comparison of donor subgroups showed that the incidence of ventricular dysfunction did not vary according to the cause of brain death. Among 27 elderly potential donors, 70% died of stroke and 85% had a diagnosis of, or risk factors for, heart disease.

Conclusions. Ventricular dysfunction accounted for 30% of cases of heart donation exclusion. Prevention or reversal of this condition could increase the heart donor pool.

Key words: *Transplantation. Donation. Myocardial contraction. Brain death.*

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Análisis de los motivos de exclusión de la donación cardiaca. ¿Causas superables?

Introducción y objetivos. La escasez de donantes cardiacos limita la expansión de los programas de trasplante. Nuestro objetivo es valorar el impacto de las diferentes causas de exclusión de la donación cardiaca y analizar potenciales aspectos superables.

Pacientes y método. Estudio descriptivo, retrospectivo, en el que se incluye a los donantes de órganos de un hospital durante 10 años. Consideramos como potenciales donantes cardiacos a los varones menores de 50 años y a las mujeres menores de 55 años. Analizamos las causas de muerte encefálica y las razones de exclusión inicial de la donación o su posterior rechazo.

Resultados. Evaluamos a 130 donantes, 69 de ellos considerados potenciales donantes cardiacos. En total 39 fueron donantes efectivos de corazón (el 30% de todos los donantes y el 56,5% de los que, por criterios de edad, podrían haber llegado a serlo). Trece donantes fueron excluidos por antecedentes de cardiopatía, la mayoría en el grupo fallecido por accidente cerebrovascular (ACVA), excepto los que tenían rotura de aneurisma o malformación ($p < 0,005$). Once donantes fueron excluidos por disfunción ventricular, en 10 probablemente secundaria a la muerte encefálica. Esta disfunción ventricular supuso el 30% de los motivos de exclusión de la donación. No hubo diferencias en la incidencia de disfunción ventricular cuando se comparó a los grupos con distintas causas de muerte encefálica. Entre los 27 potenciales donantes de edad avanzada, el 70% falleció por ACVA y en el 85% había un diagnóstico de cardiopatía o presentaba factores de riesgo para tenerla.

Conclusiones. La disfunción ventricular supone el 30% de las exclusiones de la donación cardiaca. La prevención o reversión de este fenómeno podría aumentar la reserva de donantes cardiacos.

Palabras clave: *Trasplante. Donación. Contracción miocárdica. Muerte encefálica.*

INTRODUCTION

In recent years, we have been observing a decrease in the number of heart transplantations being performed in Spain, despite the annual increase in the organ donor pool. The expectations of an increase in this type of transplantation have been frustrated and, in the past 2 years, it has been impossible to overcome the barrier of

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ABBREVIATIONS

HI: head injury.
HT: hypertension.
ICH: intracranial hemorrhage.

300 interventions. Although the mortality among patients waiting for a heart transplant remains stable, at around 9% to 12% annually,[1] we can not overlook the fact that the progressive decrease in the number of donors is already a problem. A recent report of the activities of the Spanish National Transplant Organization states that the number of patients included each year in the list is greater than the number of transplantations performed, a situation that prolongs the time spent on the waiting list and reduces the probability of a patient undergoing transplantation within the year of inclusion in the list.[2] Moreover, the number of urgent transplantations is increasing progressively and inexorably, a circumstance that also adds to the wait for patients included in the list for elective transplantation. The theoretical stability in mortality while on the waiting list may not be real, since it does not consider the deaths of patients who are excluded due to the deterioration of their clinical condition while awaiting transplantation. We also should take into account the fact that the acknowledgement of the scarcity of donors limits the entry into the program of patients with end-stage heart disease who could benefit from this technique.[3] According to studies carried out in the United States, 4000 patients are included in the waiting list each year, although 25 000 patients could be candidates for transplantation.[4] The objective of this study is to assess the impact of the different causes for excluding donor hearts and to analyze those aspects in which we could potentially increase the donor pool.

DONORS AND METHODS

We performed a descriptive, retrospective study that included all the organ donors in a tertiary hospital, with an active heart transplant program, over 10 consecutive years (1995-2004).

Men under 50 years of age and women under 55 were considered to be potential heart donors. All of them were treated according to a standardized maintenance protocol consisting in intravascular volume replacement with lactated Ringer's solution and 5% dextrose to maintain a central venous pressure of 3 to 10 mm Hg; administration of catecholamines, dopamine or noradrenaline to maintain a mean arterial pressure of 70 to 90 mm Hg; correction of fluid-electrolyte imbalances; subcutaneous or intravenous insulin administration, depending on the needs, to maintain a blood glucose level of 80 to 130 mg/dL; normalization of ventilation and oxygenation, plus intravenous desmopressin administration to control diabetes insipidus.[5] Our protocol does not include the systematic administration of glucocorticoids or thyroid hormones. Finally, to consider a heart donor suitable, we required a normal echocardiogram and a normal heart when inspected at surgery. The echocardiogram was performed by the cardiology service of our hospital. The criteria for donor acceptance and maintenance remained unchanged throughout the entire study period.

The causes of brain death were grouped as follows: head injury (HI), intracranial hemorrhage (ICH) secondary to ruptured aneurysm or vascular malformation, cerebral hemorrhage of some other origin or stroke, and others (anoxic encephalopathy, poisoning). The causes for initial exclusion from donation or subsequent rejection for implantation were analyzed. The reasons for exclusion were grouped according to four factors: history of heart disease, echocardiographic findings, surgical findings and logistic problems (lack of a recipient due to size or blood group incompatibility).

In addition, as a strategy that could potentially increase the donor pool, we analyzed the subgroup of men between the ages of 51 and 60 years and women aged 56 to 65 years for whom we had information on the causes of brain death and presence of known heart disease or cardiac risk factors, such as hypertension (HT) and/or diabetes mellitus. As the study is retrospective, their smoking history could not be analyzed.

The results are expressed as the mean plus or minus the standard deviation, and their comparison was carried out using the χ^2 test with the Yates correction.

RESULTS

During the study period, we evaluated 130 organ donors, 79 men and 51 women, with a mean age of 49±18 years (range, 16 to 78 years). The cause of death was HI in 33 cases, ICH in 32, stroke in 58, anoxic encephalopathy in 5, and methanol poisoning in 2.

Sixty-nine of these individuals, 42 men and 27 women with a mean age of 35±12 years (range, 16 to 56 years) were considered potential heart donors on the basis of age. The causes of brain death in this subgroup were HI in 26 cases, ICH in 24, stroke in 14, anoxic encephalopathy in 4, and methanol poisoning in 1. In all, 39 ultimately came to be heart donors, corresponding to 30% of all the organ donors and 56.5% of those who met the age criterion for donation. Figure consists of a flow chart illustrating the different reasons for exclusion from heart donation up until the final selection. Thirteen potential donors were excluded because of a history of heart disease or cardiac risk factors, 4 of them due to cardiac arrest secondary to heart disease, 4 because of hypertensive heart disease, 2 because of long-standing type 1 diabetes, 2 because of valve disease, and 1 because of his or her medical history.

TABLE 1. Characteristics That Differentiate Between Accepted and Rejected Potential Heart Donors*

Cause of Death	Rejected Donors				Accepted Donors			
	N (%)†	Age, Mean±SD, Years	Sex (% Males)	Catecholamines$ (%)	N (%)†	Age, Mean±SD, Years	Sex (% Males)	Catecholamines$(%)
Head injury	7 (27)	31±12	85.7	100	19 (73)	30±11	73.7	89
ICH	7 (29)	36±14	42.8	100	17 (71)	35±13	52.9	88
Stroke	11 (79)‡	43±9‡	45.4	73	3 (21)‡	49±4‡	33.3	100
Others	5 (100)‡		35±11	80	100	0		
Total	30 (43.5)	37±12	60	90	39 (56.5)	34±13	62	90

*ICH indicates intracranial hemorrhage; SD, standard deviation.
†Percentage of rejected or accepted donors in each subgroup.
‡*P*<.05 compared with the head injury and intracranial hemorrhage groups.
$Percentage of donors that received catecholamines during maintenance.

TABLE 2. Reasons for Exclusion From Heart Donation According to Cause of Death*

Cause of Death	No. Potential Donors	Causes for Exclusion			
		History	Echocardiogram†	Surgical Findings	Logistics
Head injury	26	1	4 (16%)	2‡	0
ICH	24	0	4 (17%)	2$	1
Stroke	14	8	1 (17%)	1‖	1
Others	5	4	0	0	1
Total∏	69	13 (19%)	9 (13%)	5 (7%)	3 (4%)

*ICH indicates intracranial hemorrhage.
†Incidence of ventricular dysfunction after exclusion of donors with a history of heart disease.
‡One due to myocardial contusion and 1 due to evidence of sepsis in the donor.
$One due to abnormal myocardial contraction and 1 due to cardiac arrest during harvest.
‖Due to cardiac arrest during harvest.
∏Percentage of exclusions in the group of potential donors (n=69).

There were 3 exclusions for logistic reasons, 2 due to a considerable disproportion between the size of the donor and the possible recipients and 1 because there were no recipients with the same blood group. Table 1 shows the percentage of selected donors according to cause of death, as well as the characteristics that differentiate these donors from those who were excluded, and Table 2 shows the causes for exclusion according to the origin of brain death.

In the data displayed here, there are 3 notable aspects: *a)* the majority of the excluded potential heart donors died of stroke (*P*<.005) or "other causes" (*P*<.005) (Table 1); *b)* 13 donors were ruled out because of a history of heart disease; in the majority of them, brain death was secondary to stroke; 57% of this group (8 of 14) was excluded for this reason, versus 2% (1/50) of those whose death was due to HI or ICH (Table 2); and *c)* 11 donors with no known heart disease or cardiac risk factors were excluded because of abnormal myocardial contraction, detected by preoperative echocardiogram in nine cases and during surgical exploration in 2; in 10 donors, this myocardial dysfunction was attributed to changes in contraction related to brain death and, in the remaining case, to a probable myocardial contusion secondary to chest trauma. There were no significant differences in the incidence of ventricular dysfunction when the subgroups were compared in terms of the different causes of brain death (Table 2).

Twenty-nine organ donors were between 1 and 10 years older than the established age limit. Two of them were considered for donation without performing any additional diagnostic test, such as coronary arteriography (a 51-year-old man and a 56-year-old woman), and another 4 presented no known cardiac risk factors, but were ruled out because of their age. The remainder had been diagnosed as having heart disease or 1 or more cardiac risk factors. Table 3 shows the causes of death and the heart disease risk factors in this group. The data of the 2 donors who were accepted are included with those of the selected donors.

DISCUSSION

In our series, 43% of the organ donors of ages considered suitable for heart donation (30 of 69) were ruled out for donation. The most common causes for exclusion were a history of heart disease and myocardial dysfunction, the latter probably associated with brain death.

Eighteen percent of the young donors with no history of heart disease presented severe abnormalities

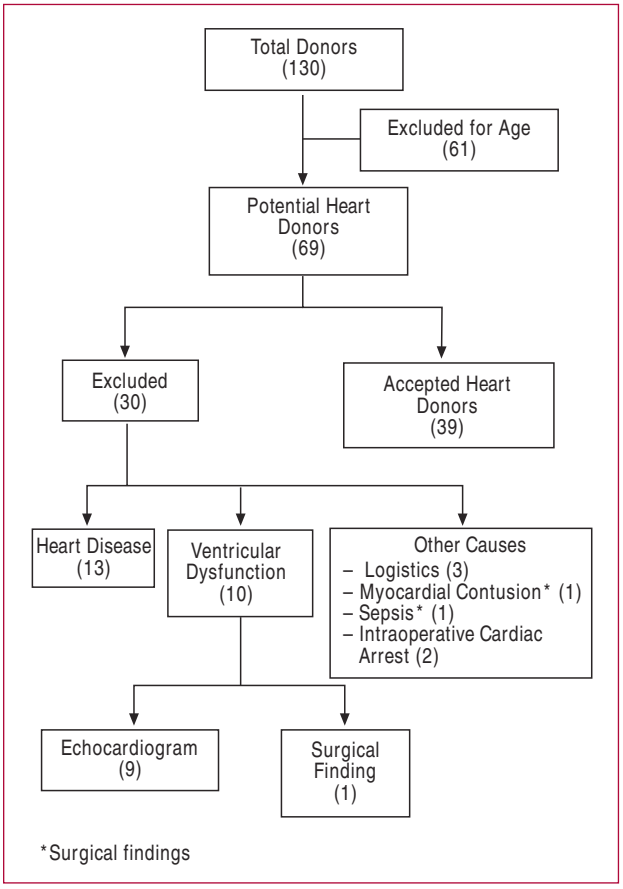

Figure. Flow chart showing heart donor selection from detection to donation.

TABLE 3. Donor Characteristics After Applying Theoretical Increase in the Age Criterion (Between 1 and 10 Years Greater Than the Established Criteria)*

Cause of Death	N	Known Heart Disease	Risk Factors	No Risk Factors
Head injury	2	1	1	0
ICH	5	2	0	3
Stroke	19	7	12	0
Others	1	0	0	1
Total	27	10 (37%)	13 (48%)	4 (15%)

*ICH indicates intracranial hemorrhage.

in myocardial contraction, probably related to the hemodynamic and neurohormonal changes that take place during brain death.[6,7] These findings are similar to those reported by other authors. For example, Gilbert et al[8] observed an incidence of 10%, Hüttemann et al[9] of 14%, Boudaa et al[10] of 21%, and Dujardin et al[11] of up to 42%. In the only Spanish study carried out in a series of 38 potential donors, Gallardo et al[12] encountered severe abnormalities in myocardial contraction that impeded donation in 19% of them. In our study, the presence of ventricular dysfunction was the cause for 30% of the cases of exclusion. This incidence is very similar to that reported recently by Zaroff et al,[13] who excluded 26% of their potential donors because of these severe changes in contractility.

Thus, the ventricular dysfunction associated with brain death appears to be one of the most common reasons for excluding donors. If it were possible to prevent, disregard or reverse this process, the donor pool would increase considerably.

With regard to prevention, although there are experimental studies on the myocardial protection provided by sympathetic block, its clinical application is very difficult and highly debatable. Only in those cases in which the brain death of the patient is inevitable and we observe the catecholamine storm *in situ* could the use of drugs with a short half-life, like esmolol, theoretically reduce myocardial injury.

With respect to the possibility of disregarding this problem, the use of hearts with abnormal myocardial contraction does not appear to be a valid option at the present time. Although there are studies that point out that the transplantation of hearts presenting ventricular dysfunction may be feasible under certain circumstances,[15-17] most authors recommend that their utilization be avoided. In the largest study published to date, ventricular dysfunction was shown to be an independent factor, unrelated to age, of early recipient mortality.[18] In fact, in the work published by Darracott-Cankovic et al,[19] the use of these hearts increased the mortality to 44%.

The most interesting aspect for study is probably the reversibility of this ventricular dysfunction. Wheeldon et al[20] demonstrated that in 92% of the hearts with impaired function according to hemodynamic variables, this problem could be reversed with a treatment protocol.[20] However, one of the factors that may have a more important influence is time. The ventricular dysfunction associated with brain death may be included among the causes of stunned myocardium and, thus, would potentially be reversible, as has been demonstrated in other entities, such as subarachnoid hemorrhage,[21] HI, or transient apical dysfunction.[22] This hypothesis has been substantiated in experimental and clinical studies.[23] For example, Zaroff et al[24] demonstrated the recoverability of ventricular function in 75% of the cases studied in serial echocardiograms. In their work, 13 of the 16 heart donors initially excluded due to ventricular dysfunction recovered ventricular function within a variable period of time and, subsequently, their hearts were successfully transplanted. However, ventricular function is not recovered in 100% of the cases, indicating that a long wait until harvest is not justified. For this reason, it would be useful to have tests that could be performed in every potential donor to discriminate between irreversible injury and stunned myocardium. The presence of electrocardiographic changes does not appear to be sensitive or specific

enough.[11] However, there are interesting studies that could aid us in decision making. For example, an enhancement of contraction after stimulation with dobutamine may identify contractile reserve in dysfunctioning zones and, thus, distinguish stunned myocardium from necrotic myocardium, as is suggested by Kono et al[25] in a series of 7 brain-dead individuals. The determination of enzyme markers of myocardial injury may also help in decision making. Riou et al[26] demonstrated the validity of troponin T and the lack of reliability of creatine kinase and its MB isoenzyme. Elevated troponin T or troponin I, in association with changes in myocardial contraction, may indicate irreversible injury or, at least, injury that is not reversible within a reasonable period of time.[25]

Given these findings, and until new data is provided, we recommend the following management strategy:

1. Prolong the interval between the performance of the echocardiogram and brain death to the greatest possible extent. With the coming into effect of the new legislation on transplantation, which will make it possible to shorten the time required for the diagnosis of brain death, a doubt has arisen in our minds: is this faster pace in the donation procedure leading to an increase in the detection of ventricular function? In our series, 8 of the 11 cases of exclusion due to ventricular dysfunction (data not shown) were detected from the year 2000 on. Moreover, we recently had a case in which heart donation was ruled out because of severe systolic dysfunction, detected after performing an echocardiogram 30 minutes after brain death; 4 hours later, during lung harvest, completely normal contraction was observed visually.

2. Perform the echocardiogram when the hemodynamic condition of the donor is stable, with a mean arterial pressure of at least 70 mm Hg. Szabo et al[23] demonstrated that maintenance of the coronary perfusion pressure is the most important factor in reversing ventricular dysfunction. To achieve this objective, it is sometimes necessary to administer dopamine or, preferably, noradrenaline.[27] We should mention that, in our series, we did not exclude any donor on the basis of the type or amount of catecholamines employed. We have shown that the use of high doses of catecholamines plays no role in early graft failure.[28] In this study, in which 27 patients were treated with high doses of catecholamines, the incidence of early graft failure was 4%.

3. Determine troponin T or I systematically to assess the myocardial injury produced during brain death. Dujardin et al[11] demonstrated that the majority of the hearts presenting ventricular dysfunction showed no microscopic changes in the pathological examination. The finding of normal or nearly normal troponin levels, in the presence of echocardiographic changes, may be indicative of minimal structural damage and justify delaying the decision as to whether to proceed with the harvest for a few hours and repeating the assessment.

A second strategy that could increase the donor pool would be to widen the age range. There are published studies that demonstrate the utility of older donors.[29] However, the findings in these studies indicate that the use of these hearts is related to an increased recipient mortality, especially when it is associated with prolonged ischemic times.[30] Del Rizzo et al[31] reported one-year and two-year mortalities of 37% and 50%, respectively, when hearts from donors over 50 years of age were employed. The heart of the older donor presents morphological changes (hypertrophy, valve sclerosis, increased collagen and lipid contents, mitochondrial calcifications), functional changes (decreases in the number and response of beta-adrenergic receptors) and an increase in the incidence of coronary artery disease.[32] In our series, 85% of the donors of an age between 1 and 10 years greater than those of the previously established criteria presented a known heart disease or 1 or more coronary risk factors. Moreover, 70% of these potential donors died of stroke, a condition that, among young donors, was the cause of brain death that most frequently resulted in exclusion from heart donation. Thus, the acceptance of donors of this type would almost inevitably involve the performance of coronary arteriography to rule out the presence of coronary artery disease. The potential increment in the donor pool that widening the age range would produce is not known, but we should remember that this diagnostic test is not available in every center or on a 24-hour basis. Thus, we consider that donors of this type could only be accepted by centers with heart transplant programs in which the recipients have a long wait. It has been demonstrated that the risk of death associated with the transplantation of an organ from an older donor is lower than that associated with a prolonged wait.[33] Moreover, to avoid prolonged ischemia, theoretically, the donors could only come from centers with access to emergency coronary arteriography that are close to the transplant center. The progressive increase in the number of requests for primary angioplasty received in the catheterization laboratories represents an opportunity to study the possible increase in the heart donor pool through this channel.

Clinical Implications

One of the most attractive fields of study involved in the attempt to increase the heart donor pool is that focusing on individuals with ventricular dysfunction secondary to brain death or to previous severe brain injury. It is difficult to calculate the probable increment in the number of transplantations that would result from their utilization. We need a nationwide registry that reflects the incidence of this problem, as well as studies

that clarify the aspects that play a role in their detection and their potential reversibility. With the obvious limitations of our study (retrospective, small sample, and extended selection period), and in a highly simplistic way, assuming that our population of 130 donors (mean age, 49±18 years) is a reflection of the scenario in the rest of Spain (1443 donors with a mean age of 48±20 years),[2] 111 potential heart donors will be rejected annually because of ventricular dysfunction. Of these, around 50% to 75%, that is 55 to 82 organs, could be usable.

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