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Performing diagnostic coronary angiography to evaluate high-risk cardiac donors: A French nationwide cohort study☆

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ABSTRACT

Background: Allograft shortage might be overcome by the use of hearts from expanded-criteria donors (ECD) but their estimated high-risk of coronary artery disease (CAD) results in a limited utilization of these hearts for transplantation. We aimed to determine if performing coronary angiography (CA) in ECD enhances cardiac procurement and to develop a predictive model estimating their probability of absence of CAD.
Methods: We retrospectively used the French National Transplant Registry CRISTAL and considered all donors aged 45 to 70 with ≥ 1 organ harvested between March 2012 and June 2014 to derive a high-risk donor population. Of 515 donors with ≥ 1 CAD risk factor and no obvious contraindication for cardiac procurement, 230 underwent CA. Coefficients estimated by multivariate logistic regression models were used to evaluate the impact of CA on procurement and build the predictive model.
Results: Among CA donors, 133 had CAD, 53 (23%) with at least one stenosis ≥ 50%. Predictors of cardiac graft offer were female gender, age below 60, no cardiac arrest, no intravenous adrenaline/dobutamine requirement and no treated hypercholesterolemia. CA increased the probability of procurement by 9% ($p = 0.028$). Female gender, non-vascular cause of death, absence of diabetes and BMI ≥ 25 kg/m^2 ($p < 0.05$) were associated with a normal CA and used for the prediction model. The area under the ROC curve of the model was 0.70. Specificity for the highest quartile was 82%.
Conclusion: Performing CA in ECD enhances cardiac procurement. When CA is not feasible, we defined a clinical score allowing accurate estimation of normal CA probability.

1. Introduction

Heart transplantation is the gold standard treatment in end-stage heart failure patients when there is no remaining therapeutic option. Optimal medical treatment and resynchronization therapy improved the management of these patients whose life expectancy increases. Early coronary revascularization of acute myocardial infarction patients reduced early cardiac deaths. Consequently, since 2005, there is a growing number of heart failure patients that are potential candidates for heart transplantation [1]. Yet the number of donors remains stable if not decreases with the advances in road safety. The waiting time was significantly longer in 2015 than during the previous decade according to the International Society for Heart and Lung Transplantation (ISHLT) registry, with a median waiting time of 144 days [2], and approximately one out of five patients dies without transplantation due to grafts shortage [3]. Concurrently with the management of acute graft rejection and immunosuppression complications, the actual main challenge is the reduced availability of grafts. The chronic shortage of heart donors led to a necessary reassessment of the suitability of potential donors and to consider older donors. As a result, the average age of donors increased over the decade from 32 [15–54] in 2003 to 35 [17–58] in the 2009–2016 period according to the ISHLT registry [4]. Heart graft donor age particularly increased in France from 39.5 to 43.3 between 2009 and 2016 [5], where young donors dying of head trauma are usually less frequent than in the USA.

Increased donor age is associated with the presence of cardiovascular risk factors and rising coronary artery disease (CAD) prevalence. Therefore, there is a greater risk for donor-transmitted coronary atherosclerosis

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1
Characteristics of all the 515 included donors according to coronary angiography group (performed or not).

	Total (n = 515)		Reviewed coronary angiography				
			No (n = 285)	%	Yes (n = 230)		p-Value
	n	%	n		n	%	
Gender (female)	211	41	112	39,3	99	43	0.390
Blood type							0.959
A	216	41,9	118	41,4	98	42,6	
AB	19	3,7	11	3,9	8	3,5	
B	51	9,9	27	9,5	24	10,4	
O	229	44,5	129	45,3	100	43,5	
Age (≥ 60 years)	258	50,1	142	49,8	116	50,4	0.891
BMI (< 25 kg/m^2)	216	41,9	134	47	82	35,7	0.009
Comorbidities							
Diabetes mellitus	66	12,8	26	9,1	40	17,4	0.005
Hypertension	237	46	130	45,6	107	46,5	0.837
History of smoking	226	43,9	123	43,2	103	44,8	0.712
Hyperlipidemia	97	18,8	46	16,1	51	22,2	0.082
Family history of premature CVD	18	3,5	8	2,8	10	4,3	0.344
History of vascular disease[a]	57	11,1	29	10,2	28	12,2	0.472
Cause of death (vascular)	349	67,8	192	67,4	157	68,3	0.829
Cardiac arrest (yes)	97	18,8	46	16,1	51	22,2	0.082
Mean arterial blood pressure (> 70 mmHg)	89	17,3	50	17,5	39	17	0.861
Serum sodium (mmol/L)							0.072
<140	87	16,9	47	16,5	40	17,4	
[140–149]	258	50,1	132	46,3	126	54,8	
≥150	170	33	106	37,2	64	27,8	
Last creatinine (< 120 μmol/L)	446	86,6	248	87	198	86,1	0.758
Hemoglobin level (< 8 g/dL)	19	3,7	11	3,9	8	3,5	0.819
Echocardiography							0.106
Normal	301	58,4	157	55,1	144	62,6	
Abnormal[b]	149	28,9	85	29,8	64	27,8	
Unknown	65	12,6	43	15,1	22	9,6	
Noradrenaline dose (mg/h)							0.588
None	83	16,1	51	17,9	32	13,9	
< 1	184	35,7	97	34	87	37,8	
[1–3]	196	38,1	107	37,5	89	38,7	
> 3	52	10,1	30	10,5	22	9,6	
Adrenaline/dobutamine (yes)	17	3,3	9	3,2	8	3,5	0.840

[a] Ischemic stroke including cause of death or lower limbs peripheral artery disease revascularization.
[b] Left-ventricular ejection fraction <50% or interventricular septal thickness >12 mm.

(DTCA), which may dramatically impact recipients' survival [6,7]. DTCA is a risk factor for primary graft dysfunction and seems to increase the risk of allograft vasculopathy, a major cause of morbi-mortality in heart transplant recipients [8–11]. Primary graft failure is mostly associated with older donor age and non-head trauma as donor cause of death, particularly in Europe [4,12]. Female gender, BMI and absence of diabetes were not associated with an increased risk for primary graft failure in several studies [9,13], yet donor diabetes mellitus was predictive of increased recipient mortality [14]. According to Eurotransplant scores, the 3-year post-transplantation survival rates was 81% in donors with normal coronary angiography (CA), compared to 50% in those with pre-established CAD [15]. Grauhan et al. showed a direct relation between the severity of DTCA and recipients' short-term outcomes, with a 30-day mortality rate of up to 61.5% in patients transplanted with double- or triple-vessel disease grafts. Therefore, the Association of Organ Procurement Organizations Consensus Statement in the USA recommends performing CA in both older donors (≥40 years) and younger donors with additional cardiovascular risk factors [16,17]. The Canadian Council for Donation and Transplantation [18] and the Council of Europe [19] also recommend routine CA donor screening in donors at risk of cardiovascular diseases due to their age and/or risk factors, yet the impact of CA practice in these expanded-criteria donors (ECD) on graft acceptance was never assessed.

According to observational data, about 30% of ECD hearts are accepted for transplantation without prior CA in the USA. Their recipients generally have poor prognosis [20]. In Europe, particularly in France where cardiovascular mortality rates are low [21], CA is not considered mandatory in the decision process of cardiac procurement in donors aged over 45. Transplant teams often request it on a case-to-case basis in ECD but this investigation cannot always be performed due to the difficulty of access to CA that raises the issues of distribution of infrastructures, financial and human resources. Consequently, ECD who can't access CA may not be considered eligible for heart procurement, thereby decreasing the number of potential graft.

This study aimed to determine if performing a diagnostic CA enhances cardiac procurement in ECD. Our secondary objective was the development of a clinical score to estimate as accurately as possible the probability of absence of CAD in ECD, based on the anamnestic, clinical and angiographic characteristics of a population of French donors with high cardiovascular risk profile. This predictive score could be used whenever CA is not accessible and could increase the number of grafts with an acceptable level of risk for the recipient, though every effort should be made to provide access to CA to ECD as it dramatically increases the rate of cardiac procurement.

2. Methods

2.1. Study design and eligibility criteria

In this nationwide cohort study, all brain-dead donors aged 45 to 70 with at least one organ harvested between March 2012 and June 2014 were screened for CAD risk factors

Notes to Table 2:
CI: confidence interval; BMI: Body mass index; CVD: Cardiovascular disease. C-index = 0.69.
[a] Ischemic stroke including cause of death or lower limbs peripheral artery disease revascularization.

Table 2
Univariate and multivariable logistic regression for cardiac offer to transplant teams among 515 included donors.

Characteristics	n	% event	Univariate analysis			Multivariable analysis		
			OR	CI (95%)	p-Value	OR	CI (95%)	p-Value
Gender								
Male	304	85.2	1	–		1	–	
Female	211	90.05	1.57	0.91–2.73	0.11	1.98	[1.11–3.51]	0.02
Blood type								
A	216	87.04	1.05	0.61–1.82	0.86			
AB	19	84.21	0.84	0.23–3.03	0.78			
B	51	92.16	1.84	0.62–5.46	0.27			
O	229	86.46	1	–				
Age (years)								
< 60	257	91.05	2.03	1.19–3.49	0.01	2.51	[1.42–4.44]	0.002
≥ 60	258	83.33	1	–		1	–	
BMI (kg/m^2)								
< 25	216	88.89	1.31	0.77–2.23	0.33			
≥ 25	299	85.95	1	–				
Diabetes mellitus								
No	449	87.75	1	–				
Yes	66	83.33	0.7	0.34–1.41	0.32			
Hypertension								
No	278	88.13	1	–				
Yes	237	86.08	0.83	0.50–1.40	0.49			
History of smoking								
No	289	86.16	1	–				
Yes	226	88.5	1.24	0.73–2.09	0.43			
Hyperlipidemia								
No	418	88.52	1	–		1	–	
Yes	97	81.44	0.57	0.31–1.03	0.06	1.96	[1.06–3.62]	0.033
Family history of premature CVD								
No	497	87.12	1	–				
Yes	18	88.89	1.18	0.27–5.26	0.83			
History of vascular disease[a]								
No	458	87.34	1	–				
Yes	57	85.96	0.89	0.40–1.97	0.77			
Cause of death								
Vascular	349	87.39	1	–				
No vascular	166	86.75	0.94	0.55–1.63	0.84			
Cardiac arrest								
No	418	89	1	–		1	–	
Yes	97	79.38	0.48	0.27–0.85	0.012	0.49	[0.26–0.91]	0.024
Mean arterial blood pressure (>70 mmHg)								
No	89	87.64	1.05	0.53–2.10	0.89			
Yes	426	87.09	1	–				
Serum sodium (mmol/L)								
<140	87	83.91	0.61	0.30–1.22	0.16			
[140–149]	258	89.53	1	–				
≥150	170	85.29	0.68	0.38–1.21	0.19			
Last creatinine (<120 μmol/L)								
No	446	87.22	1	–				
Yes	69	86.96	0.98	0.46–2.08	0.95			
Hemoglobin level (g/dL)								
< 8	19	94.74	2.71	0.36–20.7	0.34			
≥ 8	496	86.9	1	–				
Noradrenaline dose (mg/h)								
None	83	90.36	1.43	0.62–3.31	0.4			
<1	184	88.59	1.19	0.64–2.19	0.58			
[1–3]	196	86.73	1	–				
>3	52	78.85	0.57	0.26–1.25	0.16			
Adrenaline/dobutamine								
No	498	87.75	1	–		1	–	
Yes	17	70.59	0.33	0.11–0.98	0.047	0.3	[0.09–0.96]	0.043
Result of coronarography confirmed by experts								
No	285	88.42	1	–		1	–	
Yes	230	85.65	0.78	0.47–1.31	0.35	0.84	[0.49–1.44]	0.53

Table 3
Univariate and multivariable logistic regression for cardiac procurement among 449 donors offered to transplant teams.

Characteristics	n	% event	Univariate analysis			Multivariable analysis		
			OR	CI (95%)	p-Value	OR	CI (95%)	p-Value
Gender								
Male	259	70.66	1	–				
Female	190	64.74	0.76	0.51–1.14	0.18			
Blood type								
A	188	73.4	8.28	2.55–26.9	0.0004	7.96	[2.38–26.7]	0.001
AB	16	25	1	–		1	–	
B	47	53.19	3.41	0.96–12.1	0.06	3.23	[0.88–11.9]	
O	198	70.2	7.07	2.19–22.8	0.001	6.65	[2.00–22.1]	
Age (years)								
< 60	234	77.78	1	–		2.74	[1.78–4.24]	< 0.0001
≥ 60	215	57.67	0.39	0.26–0.59	< 0.0001	1	–	
BMI (kg/m^2)								
≥ 25	257	70.43	1	–				
< 25	192	65.1	0.78	0.53–1.17	0.23			
Diabetes mellitus								
No	394	68.02	1	–				
Yes	55	69.09	1.05	0.57–1.93	0.87			
Hypertension								
No	245	67.35	1	–				
Yes	204	69.12	1.09	0.73–1.62	0.69			
History of smoking								
No	249	66.67	1	–				
Yes	200	70	1.17	0.78–1.74	0.45			
Hyperlipidemia								
No	370	68.65	1	–				
Yes	79	65.82	0.88	0.53–1.47	0.62			
Family history of premature CVD								
No	433	67.9	1	–				
Yes	16	75	1.42	0.45–4.48	0.55			
History of vascular disease[a]								
No	400	68.5	1	–				
Yes	49	65.31	0.87	0.46–1.62	0.65			
Cause of death								
Vascular	305	67.54	1	–				
No vascular	144	69.44	1.09	0.71–1.68	0.69			
Cardiac arrest								
No	372	67.74	1	–				
Yes	77	70.13	1.12	0.66–1.91	0.68			
Result of echocardiography								
Normal	267	71.91	1	–		1	–	
Abnormal[b]	122	64.75	0.72	0.45–1.13	0.16	0.72	[0.44–1.17]	0.08
Unknown	60	58.33	0.55	0.31–0.98	0.041	0.51	[0.28–0.95]	
Mean arterial blood pressure (>70 mmHg)								
No	78	64.1	0.8	0.48–1.34	0.4			
Yes	371	69	1	–				
Serum sodium (mmol/L)								
< 140	73	57.53	0.59	0.34–1.01	0.06			
[140–149]	231	69.7	1	–				
≥ 150	145	71.03	1.07	0.68–1.68	0.78			
Last creatinine (< 120 μmol/L)								
No	389	68.12	1	–				
Yes	60	68.33	1.01	0.56–1.81	0.97			
Hemoglobin level (g/dL)								
< 8	18	77.78	1.67	0.54–5.15	0.38			
≥ 8	431	67.75	1	–				
Noradrenaline dose (mg/h)								
None	75	68	1	–				
< 1	163	74.85	1.4	0.77–2.55	0.27			
[1–3]	170	64.71	0.86	0.48–1.54	0.62			
> 3	41	56.1	0.6	0.27–1.32	0.2			

Table 3 (*continued*)

Characteristics	n	% event	Univariate analysis			Multivariable analysis		
			OR	CI (95%)	p-Value	OR	CI (95%)	p-Value
Adrenaline/dobutamine								
No	437	68.65	1	–		1	–	
Yes	12	50	0.46	0.14–1.44	0.18	0.3	[0.09–0.99]	0.048
Result of coronarography confirmed by experts								
No	252	64.29	1	–		1	–	
Yes	197	73.1	1.51	1.00–2.27	0.047	1.6	[1.03–2.47]	0.035

CI: confidence interval; BMI: Body mass index; CVD: Cardiovascular disease. C-index = 0.70.
[a] Ischemic stroke including cause of death or lower limbs peripheral artery disease revascularization.
[b] Left-ventricular ejection fraction <50% or interventricular septal thickness >12 mm.

and suitability for cardiac procurement. Donors aged 45 to 55 years with at least two CAD risk factors or aged 56 to 60 years with at least one CAD risk factor or >60 years were included in the study. CAD risk factors used for inclusion were: age >50 years for men and >60 years for women; current or past smoking habits; family history of premature CAD in a first-degree <55 years male or <65 years female relative; diabetes mellitus; treated hypercholesterolemia; treated arterial hypertension; established atherosclerotic vascular disease (ischemic stroke including cause of death, lower limbs peripheral artery disease revascularization). Donors fulfilling any of the following criteria were considered not suitable for heart procurement and excluded from the study: known CAD; left ventricular ejection fraction <45%; cardiac hypertrophy defined as septal wall thickness ≥15 mm; any other significant structural echocardiographic abnormalities; cardiac trauma; unstable hemodynamics despite treatment optimization; patients or close relatives choice to opt out of cardiac donation.

2.2. Data source and variables

CRISTAL is a national database administered by the national transplant authority "Agence de la biomédecine (ABM)" that prospectively collects data on all identified potential brain-dead organ donors in France along with the allografts outcomes. Data are filled in by the hospital transplant coordinators under the responsibility of the ABM physicians who decide whether or not organs are suitable for transplantation. Data collection is mandatory. Donor-specific variables potentially associated with graft offer and procurement as well as factors potentially associated with the presence of CAD were analyzed. Selected donor data included demographic factors, cause of death, clinical characteristics and laboratory values. CAD risk factors not specified in the original database were prospectively collected and saved in a specific database. The cause of death was entered as vascular or non-vascular. CA was performed in the procurement hospitals with a catheterization laboratory.

2.3. Coronary angiography

Two independent interventional cardiologists unaware of donor characteristics analyzed angiographies off-line. In case of discrepancy, a third expert re-analyzed CA to rule on the coronary status of the donor. For each coronary segment with an identifiable lesion, we determined the percentage of stenosis as <50% or ≥ 50%. Each stenosis ≥50% in vessels ≥1.5 mm was considered significant and used to calculate the syntax score (http://www.syntax-score.com). Based on this analysis, donors were classified into three groups: normal CA, non-significant (at least one < 50% coronary stenosis) or significant (at least one ≥ 50% coronary stenosis) angiographic disease.

2.4. Statistical analysis

Characteristics of all donors included in the study are presented as numbers and group percentages. The values were compared between the donor groups with and without CA using a chi-square test or two-sided Fisher's exact test. Multivariate logistic regression models were developed to assess the association of CA findings with cardiac offer and CA practice with cardiac procurement in donors whose heart was offered for transplantation. A multivariate logistic regression model was developed to assess the relationship between donor factors and absence of CAD in the donor group with reviewed CA. All variables associated with the absence of CAD at a p level < 0.2 in univariate analysis were entered in the multivariate analysis. The estimated coefficients of identified independent factors associated with a normal CA were used to establish a score. The area under the ROC curve was used to determine the discriminatory capability of the model. Donors were classified according to score's quartiles where Q4 reflected a high normal angiography probability. Sensitivity, specificity and predictive values for Q4 score were calculated. The associated *c-statistics* were calculated.

Statistical analyses were performed using SAS guide 5.1. The significance test was based on $p < 0.05$.

3. Results

3.1. Donors' characteristics

1825 brain-dead donors aged 45 to 70 years were screened between March 2012 and June 2014. 457 did not meet the inclusion criteria and 853 fulfilled at least one exclusion criterion, including 215 with a history of CAD. Finally, 515 potential donors were included in the study among which 230 had a CA; the absence of CA in the 285 remaining patients was usually due to the absence of a catheterization laboratory in the procurement hospital. The flow chart of donors is depicted in Supplemental Fig. 1.

Characteristics of all included donors are presented in Table 1. Overall, 50% of donors were ≥ 60 years, 46% had arterial hypertension, 44% were current or former smokers, 13% had diabetes mellitus and 19% had resuscitated cardiac arrest. Donors with and without CA had similar demographics, cause of death, inotropic requirement, frequency of structural/functional echocardiographic abnormalities and abnormal laboratory values. However, CA donors were more likely to have BMI ≥ 25 kg/m^2 (64% versus 53%, p = 0.009) and diabetes mellitus (17% versus 9%, p = 0.005).

3.2. Coronary angiography findings

CAD was detected in 133 (58%) donors; 80 (35%) had non-significant CAD, i.e. visible atheroma with < 50% stenosis, and 53 (23%) had significant CAD. Among these 53 donors, 36 (68%) had single vessel disease, including 25 with left anterior descending coronary artery stenosis, 13 (25%) donors had double vessel disease and 4 (7%) triple vessel disease. Four donors had a syntax score > 22.

3.3. Effect of performing CA on cardiac offer and procurement

Of the 515 potential cardiac donors, 449 (87%) were considered suitable for cardiac offer. 306 (68%) of the offered hearts were retrieved for transplantation, the remaining 143 (32%) were not used for transplantation. Among the 230 CA donors, 197 (86%) hearts were offered and 144 (63%) accepted for transplantation. In the 285 donors without CA, 252 (88%) hearts were offered and 162 (57%) accepted.

Univariate and multivariate analyses for predictors of cardiac offer are presented in Table 2. The independent factors associated with cardiac offer were female gender, donor age < 60 years, absence of cardiac arrest, absence of adrenaline/dobutamine requirement and absence of treated hypercholesterolemia. The model exhibited good predictive accuracy (*c-statistic* = 0.69).

Univariate and multivariate analyses for predictors of cardiac procurement in donors whose heart was offered are shown in Table 3. The independent factors associated with cardiac procurement were age < 60 years and CA whatever the result. The offer acceptance rate was 9% higher in CA donors (73%) compared to those without CA (64%). The final model showed good predictive accuracy (*c-statistic* = 0.70).

Table 4
Univariate and multivariable logistic regression used to generate normal CA score (230 donors with CA performed).

Characteristics	n	% event	Univariate analysis			Multivariable analysis		
			OR	CI (95%)	p-Value	OR	CI (95%)	p-Value
Gender								
Male	131	36.64	1	–		1	–	
Female	99	49.49	1.69	1.00–2.88	0.05	2.17	[1.22–3.86]	0.008
Blood type								
A	98	40.82	1.03	0.59–1.83	0.91			
AB	8	50	1.5	0.35–6.35	0.58			
B	24	54.17	1.77	0.72–4.35	0.21			
O	100	40	1	–				
Age (years)								
< 60	114	38.6	0.75	0.44–1.26	0.28			
≥ 60	116	45.69	1	–				
BMI (kg/m^2)								
< 25	82	28.05	0.39	0.22–0.70	0.001	0.28	[0.15–0.53]	< 0.0001
≥ 25	148	50	1	–		1	–	
Diabetes mellitus								
No	190	44.21	1	–		2.45	[1.12–5.34]	0.024
Yes	40	32.5	0.61	0.30–1.25	0.18	1	–	
Hypertension								
No	123	43.09	1	–				
Yes	107	41.12	0.92	0.55–1.56	0.76			
History of smoking								
No	127	44.09	1	–				
Yes	103	39.81	0.84	0.49–1.42	0.51			
Hyperlipidemia								
No	179	43.58	1	–				
Yes	51	37.25	0.77	0.41–1.46	0.42			
Family history of premature CVD								
No	220	42.73	1	–				
Yes	10	30	0.57	0.14–2.28	0.43			
History of vascular disease[a]								
No	202	42.57	1	–				
Yes	28	39.29	0.87	0.39–1.96	0.74			
Cause of death								
Vascular	157	37.58	1	–		1	–	
Not vascular	73	52.05	1.8	1.03–3.16	0.04	2.45	[1.33–4.53]	0.004
Cardiac arrest								
No	179	39.66	1	–				
Yes	51	50.98	1.58	0.85–2.96	0.15			
Mean arterial blood pressure (> 70 mmHg)								
No	39	35.9	0.73	0.36–1.49	0.38			
Yes	191	43.46	1	–				
Serum sodium (mmol/L)								
< 140	40	52.5	1.63	0.79–3.32	0.18			
[140–149]	126	40.48	1	–				
≥ 150	64	39.06	0.94	0.51–1.74	0.85			
Last creatinine (< 120 μmol/L)								
No	198	41.92	1	–				
Yes	32	43.75	1.08	0.51–2.29	0.85			
Hemoglobin level (g/dL)								
< 8	8	37.5	0.82	0.19–3.50	0.79			
≥ 8	222	42.35	1	–				
Noradrenaline dose (mg/h)								
None	32	43.75	1	0.44–2.25	0.99			
< 1	87	37.93	0.78	0.43–1.43	0.43			
[1–3]	89	43.82	1	–				
> 3	22	50	1.28	0.50–3.26	0.6			
Adrenaline/dobutamine								
No	222	41.44	1	–				
Yes	8	62.5	2.36	0.55–10.1	0.25			

CI: confidence interval; BMI: Body mass index; CVD: Cardiovascular disease. C-index = 0.70.
[a] Ischemic stroke including cause of death or lower limbs peripheral artery disease revascularization.

3.4. Normal coronary angiography prediction model

Predictors of normal CA are detailed in Table 4.

In univariate logistic regression model, donor BMI ≥ 25 kg/m^2 ($p = 0.001$) and non-vascular cause of death ($p = 0.04$) were significantly associated with a normal CA; female gender ($p = 0.05$), history of cardiac arrest ($p = 0.15$), sodium blood level < 140 mmol/L ($p = 0.18$) and absence of diabetes mellitus ($p = 0.18$) tended to be associated with a normal CA. In multivariate logistic regression model including all variables associated with a normal CA in the univariate model at a p level < 0.2, female gender (OR = 2.17 [1.22–3.86], $p = 0.008$), BMI ≥ 25 kg/m^2 (OR = 0.28 [0.15–0.53], $p < 0.0001$), non-vascular cause of death (OR = 2.45 [1.33–4.53], $p = 0.004$) and absence of diabetes mellitus (OR = 2.45 [1.12–5.34], $p = 0.024$) remained associated with normal CA.

Supplemental Fig. 2 shows the ROC curve of the final model (*c-statistic* = 0.70). According to each estimated coefficient of the predictors identified in the multivariate logistic regression model, we set a prediction score defined as follows:

Score = 0.7747 if female − 1.2611 if BMI < 25
+ 0.8973 if non-vascular cause of death
− 0.8948 if diabetes mellitus

In the absence of a clear cut-off for prediction of normal CA, donors were classified into quartiles. The specificity, sensitivity, positive predictive value and negative predictive value for the highest quartile, i.e. score > 0.7747, were respectively 82%, 49%, 67% and 69%. Of the 133 donors with angiographic CAD, only 18% were classified at low risk of disease by the score. Regarding the donors with significant CAD, only 12.5% were classified in Q4.

3.5. Survival in recipients of CAD grafts

Sixteen grafts out of the 53 donors with significant coronary stenosis were accepted for transplantation. Fifteen were single-vessel diseased hearts and one displayed double-vessel CAD. Eight recipients of these hearts died within the first year, one graft was transplanted to a recipient in another country with no follow-up data available.

4. Discussion

Performing CA in ECD increased cardiac graft offer acceptance by 9% in our population. In addition, female gender, non-cerebrovascular cause of death, absence of diabetes, and a BMI ≥ 25 kg/m^2 were significant predictors of normal CA in these patients.

The approach described here was justified by the need for expanding the donor pool in the general context of lack of grafts. Refusal of a heart is often explained by the presence of cardiovascular risk factors without CA performed to rule out CAD. We report here for the first time that performing CA in a high CAD prevalence donor population enhances cardiac procurement, whatever the result of CA, emphasizing the current recommendations in North America. We estimated that the number of heart procurements could be increased by approximately 9% if CA was systematically performed in ECD. This would correspond in France to a total of 40 additional end-stage heart failure patients receiving a heart over 2 years. As only 16 CAD grafts were used for transplantation, it was not possible to derive any conclusion regarding the outcomes of their recipients (≥ 50% mortality rate at one year in our cohort) who were certainly recipients with the highest risk profile. DTCA significantly worsens heart transplantation outcome [7,9,10]. Grafts with multiple vessel CAD are at serious risk of early graft failure, yet the short- and long-term prognosis of single vessel CAD hearts is not different from grafts without CAD, suggesting that these hearts may further increase the pool of available grafts [6]. CA is useful in determining donors' coronary status, thus reducing the risk of DTCA and performing systematic CA in ECD may be a real answer to organ shortage. These results should encourage all organ donation networks to recommend performing CA as part of the heart donor evaluation in high-risk patients. Our data are supported by Schmidt et al. who showed that performing CA before heart procurement improved donor screening with similar survival rates at 1-year follow-up, independently of donor age and of the degree of stenosis, in case of latent donor CAD [22]. From both a logistical and financial point of view, CA is feasible in ECD and does not compromise the donation process [23,24]. In addition, it has been shown that the infusion of contrast medium had no significant impact on kidney transplant from a CA donor [25,26].

Several reasons were reported for not performing CA, first being a difficult access to catheterization laboratories and our data showing that CA donors had similar characteristics to non-CA donors (except for upper BMI and more frequent diabetic status) plead for performing CA to be mainly an organizational issue that must be overcome. Yet the inability to perform CA should not preclude cardiac procurement. We suggest an alternative based on a normal CA predictive score that could be used whenever CA is not available. Factors associated with normal CA in our high CAD prevalence donor population were: female gender, non-cerebrovascular cause of death, absence of diabetes, and a BMI ≥ 25 kg/m^2. The association between normal CAD and BMI ≥ 25 kg/m^2 may appear counterintuitive, yet Romero-Corral et al. reported, in a systematic review of cohort studies including >250,000 patients, that overweight patients (BMI 25–29.9) were the group with the lowest cardiovascular mortality (RR = 0.88 [0.75-1-02]), obese patients (BMI 30–35) having no increase in cardiovascular mortality (RR = 0.97 [0.82-1-15]) [27]. The AUC of the model being 0.70 and the specificity for the highest normal CA score quartile 82%, this score is an innovative tool that may help reduce heart graft shortage. Using this score may facilitate DTCA risk assessment and increase the ECD heart pool with an acceptable level of risk for the recipient. At this point, it remains difficult to predict the impact of such a score on the heart pool. This score could be used in addition to other heart donor scores such as Eurotransplant that accurately reflects the likelihood of organ acceptance and predicts long-term mortality [7,15]. In case of false negative, the explanting surgeon could still detect CAD and revascularization by internal mammary coronary artery bypass grafting during the transplantation procedure or percutaneous coronary intervention after the transplantation should be considered [6,18,28].

In our study, prevalence of significant (≥ 50% stenosis) CAD in ECD was 23%. These data are consistent with the Diamond-Forrester model estimating the probability of CAD in a cohort of patients referred for CA due to chest pain history [29] and in other published studies that reported a 20% prevalence of significant atherosclerotic lesions in the ECD pool [10].

This study has some limitations. First, it is an observational study with a non-random allocation of intervention on subjects, which is likely to induce bias. Yet, while there was a valid indication of CA in every patient, its realization was conditioned by the existence of a catheterization laboratory on site and, of course, this couldn't be randomized. Performing a prospective randomized study limited to the only sites with a catheterization laboratory to assess this question may raise the risk of selecting a population different from the general population of donors. Second, the predictive score was derived from the French population and may require local adaptations, especially if donors are from countries where the prevalence of CAD differs, according to the data from the European Society of Cardiology [30]. Of course, the predictive performance of the score requires to be confirmed with a validation cohort.

In conclusion, performing CA in the high CAD prevalence donor population enhances cardiac procurement. When CA cannot be performed, a predictive model including donor gender, cause of death, absence of diabetes, and BMI may help identify patients with normal CA. We believe that our results combined with previous data and recommendations from North American health authorities should pave the way for

new international recommendations regarding the use of CA when feasible in expanded-criteria heart donors, as suggested by a recent experts' statement [31].

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Competing interests

None.

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