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MAGNETIC RESONANCE

Point estimate and reference normality interval of MRI-derived myocardial extracellular volume in healthy subjects: a systematic review and meta-analysis

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Abstract

Objectives To estimate the MRI-derived myocardial extracellular volume (ECV) in healthy subjects together with reference normality interval.

Methods The study was registered on PROSPERO and reported according to PRISMA. In October 2017, a systematic search (MEDLINE/EMBASE) was performed for articles reporting MRI-derived ECV in healthy subjects. The pooled ECV (pECV) with 95% confidence interval (CI) was calculated using the random-effect model; the normality interval was calculated as pECV ± 2 root mean square of all study standard deviations. The Newcastle-Ottawa scale was used for assessing study quality, subgroup/meta-regression analyses for technical/biological covariates, and Egger test for publication bias risk.

Results Of 282 articles, 56 were analyzed totaling 1851 subjects with age 16–68 years, body mass index 23–28 kg/m^2, and left ventricular ejection fraction 58–74%. Contrast dose varied from 0.075 to 0.200 mmol/kg. Heterogeneity was high ($I^2 = 92\%$). The pECV was 25.6% (95% CI 25.2–26.0%) with a normality interval of 19.6–31.6%. pECV was slightly increasing with age ($\beta = 0.03\%$, $p = 0.038$) and slightly decreasing with the percentage of males ($\beta = -0.02\%$, $p = 0.053$). Sequence type significantly ($p = 0.003$) impacted on pECV: the normal interval was 19.9–31.9% for MOLLI and 20.3–33.5% for ShMOLLI. Contrast type/dose, time of acquisition, and magnetic field strength did not significantly impact pECV ($p > 0.093$). Quality was moderate or high in 48/56 studies (86%). No risk of publication bias ($p = 0.728$).

Conclusions Myocardial pECV in healthy subjects was 25.6%, increasing by 0.03% for each year of age. The ECV normality interval was 19.9–31.9% for MOLLI and 20.3–33.5% for ShMOLLI.

Key Points
- *The pooled estimate of normal MRI-derived ECV based on 1851 subjects was 25.6%, slightly increasing with age and slightly decreasing with the percentage of males.*
- *MRI-derived ECV was independent of contrast type/dose and field strength but dependent on the imaging sequence.*
- *The modeled normality reference interval of MRI-derived ECV was 19.9–31.9% for the MOLLI sequence and 20.3–33.5% for the ShMOLLI sequence.*

Keywords Magnetic resonance imaging · Meta-analysis · Fibrosis · Cardiomyopathies · Biomarkers

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Abbreviations

CI	Confidence interval
ECV	Extracellular volume
LGE	Late gadolinium enhancement
MOLLI	Modified Look-Locker inversion recovery
MRI	Magnetic resonance imaging
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
SD	Standard deviation
ShMOLLI	Shortened modified Look-Locker inversion recovery

Introduction

Non-invasive evaluation of myocardial tissue is a major goal of cardiac imaging. This is the case of myocardial fibrosis that plays a crucial role in many myocardial diseases, with ischemic or non-ischemic pathogenesis [1–3]. The reference standard is the histology obtained by myocardial biopsy, but it is associated with high invasiveness as well as with a non-negligible risk of complications [4–6] and sampling errors, especially in case of focal fibrosis [7, 8].

Contrast-enhanced magnetic resonance imaging (MRI) with late gadolinium enhancement (LGE) offers the possibility of a non-invasive assessment of fibrosis after myocardial infarction [9], with a prognostic value higher than that of clinical risk scores or left ventricular ejection fraction [10]. However, LGE imaging is limited to the study of end-stage, irreversible, focal fibrosis. To overcome these limitations, new techniques were introduced based on measurements of the T1 longitudinal relaxation time of the myocardium, which can detect diffuse myocardial changes not amenable to visual detection: the so-called native T1 mapping and the quantification of extracellular volume (ECV). The latter is obtained after contrast agent injection, taking into account the value of hematocrit [11, 12]. In practice, the larger the ECV, the more contrast agent entering this space that, in turn, results in a reduced T1 [13, 14].

Notably, ECV is a sensitive biomarker for myocardial alterations also in the presence of pathologic conditions other than fibrosis [15–18]. It has been reported to be significantly increased in acute myocardial infarction, myocarditis and Takotsubo cardiomyopathy (with edematous interstitium), hypertrophic cardiomyopathy (with myocyte disarray combined with diffuse fibrosis), and amyloid deposition (in the interstitium); of note, ECV is not expanded in Anderson-Fabry disease and in iron-overload cardiomyopathy, while it is reduced in lipomatous metaplasia [12, 19].

In addition, the expansion of ECV has been proven to be a risk factor for arrhythmia, heart failure, and sudden cardiac death in patients with acute or chronic myocardial infarction, hypertrophic cardiomyopathy, or aortic valve disease [20–24]. Finally, ECV has been also proven to be a good predictor of regional and global left ventricular functional recovery in patients with acute myocardial infarction [22].

Like all other medical measurements such as blood tests, the ECV also needs to be referred to normal values that are measured in healthy subjects. In literature, many articles on small series have provided such a normal value, although with large 95% confidence intervals (CIs). Theoretically, a large population-based study would be the right approach to define reference normality intervals of myocardial ECV. However, this is not easy to be performed. In our study, we tried to overcome this limitation by using the methodology of systematic reviews and meta-analysis. Meta-analyses are typically used to accurately estimate the central value of a given end-point, together with its 95% CI. In this study, we exploited the information brought by the study-level standard deviation (SD) to model a virtual population variability of ECV.

The aim of this systematic review and meta-analysis was to provide a precise estimate of the mean ECV in healthy subjects, together with a reference normality interval.

Materials and methods

Study protocol

No ethics committee approval was needed for this systematic review. The study protocol was registered on PROSPERO (registration, CRD42017067360), the international prospective register of systematic reviews [25]. This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [26].

Search strategy and study eligibility criteria

In October 2017, a systematic search was performed using MEDLINE (PubMed, www.pubmed.gov) and EMBASE (Elsevier) for articles providing MRI-derived myocardial ECV in healthy subjects. A controlled vocabulary (medical subject headings in PubMed; thesaurus keywords in EMBASE) was used. Keywords included ECV, T1 mapping, heart muscle fibrosis, molli/shmolli, and MRI.

The search was limited to original articles published in English in peer-reviewed journals and with an available abstract. Studies in vitro or on animal models as well as those using synthetic hematocrit for ECV calculation were excluded. No limits were applied to publication date.

The initial screening of eligible articles was performed by two independent readers (with 3 and 2 years of experience with cardiac MRI) based only on title and abstract. Eligible articles were those that reported in the abstract the mean ECV and SD in healthy subjects or that could have contained these data in the manuscript. After downloading eligible articles, the full text was read for a complete assessment. Finally, references of included articles were hand-searched to check for further eligible studies. In case of disagreement, arbitrate was performed by a third reader with 10 years of experience in biomedical research.

Data extraction

Data extraction was performed independently by the same two readers who performed the literature search. Disagreements were settled by discussion with the third reader. For each analyzed article, journal, year of publication, study design, number of subjects, and demographics were recorded. Body mass index and left ventricular ejection fraction were the extracted clinical data. Magnetic field strength and imaging sequence protocol were also noted as well as type, dose, and acquisition timing after the injection of the contrast agent.

Statistical analysis

Statistical analysis was performed using R (version 3.3.3; package metaphor in R; R Foundation for Statistical Computing) and Comprehensive Meta-Analysis v2.2.057 (Biostat). I^2 statistics was first calculated, which provided an estimate of the degree of variance due to heterogeneity rather than chance [27, 28]. The random-effect model with the DerSimonian and Laird method, suitable for handling heterogeneous data [29], was used to calculate the pooled ECV and 95% CI.

The potential sources of heterogeneity were evaluated by subgroup or meta-regression analyses. In particular, subgroup analyses were performed by considering the effect on ECV of the magnetic field strength, imaging sequence protocol, and type of contrast agent. Meta-regression analyses were performed to investigate for the year of publication, subjects' age, percentage of males, body mass index, left ventricular ejection fraction, dose of contrast agent, acquisition time after contrast agent injection, and time of echo and time of repetition of the sequence protocol. Only significant covariates were introduced in a multivariate meta-regression analysis. To account for multiple testing, the Benjamini-Hochberg method was applied [30].

The reference intervals for normal ECV were calculated under the assumption of normality. Such an assumption seems reasonable looking, for example, the boxplot of the ECV distribution published in Storz et al [31], which looks quite symmetric. A pooled SD was calculated as the root mean square of all study SDs, taking into account each study sample size [32]. The interval of normality for ECV was calculated as pooled ECV ± 2 × pooled SD. When applicable, this reference interval was calculated in subgroups.

The risk of publication bias was assessed by visually inspecting funnel plots and performing the Egger test [33].

Quality appraisal

Methodological quality of analyzed studies was evaluated using the Newcastle-Ottawa Scale [34] by the same two independent reviewers who extracted the data; arbitrate was performed by the same third author. Considering that a score of 9 represented the highest quality, a score of ≥ 7 indicated high quality, a score from 4 to 6 indicated moderate quality, and scores ≤ 3 indicated low quality [35].

Results

Literature search and characteristics of the analyzed studies

The flowchart of the literature search is shown in Fig. 1. From the initial search, 282 articles were retrieved, 56 of them being analyzed [17, 31, 36–89]. All articles were prospective; six had an intra-individual study design with patients studied twice [42, 45, 48, 68] or three times [51, 83]. Those study parts were considered independent and the statistical analysis was performed on a total of 64 study parts.

The number of healthy subjects ranged from 7 [43] to 218 [31], for a total of 1851 healthy subjects. Healthy subjects were volunteers or subjects with no history of cardiac disease and free of symptoms in 41 of 56 articles; the remaining 15 articles only indicated that the studied subjects were healthy controls in a case-control study. Mean age ranged from 15 [81] to 68 years [36]. All studies evaluated normal-weight or slightly overweight subjects, with a body mass index from 20 [81] to 28 kg/m^2 [60].

All subjects were in apparently good cardiac condition, with a left ventricular ejection fraction ranging from 58% [37] to 74% [69]. Magnetic field strength was 1.5 T in 38/64 (59%) study parts, 3 T in 25/64 (39%), and mixed in 1/64 (2%). Of 64 study parts, 46 (72%) used a modified Look-Locker inversion recovery (MOLLI) sequence, 4 (6%) used the shortened MOLLI (ShMOLLI) sequence, and 14 (22%)

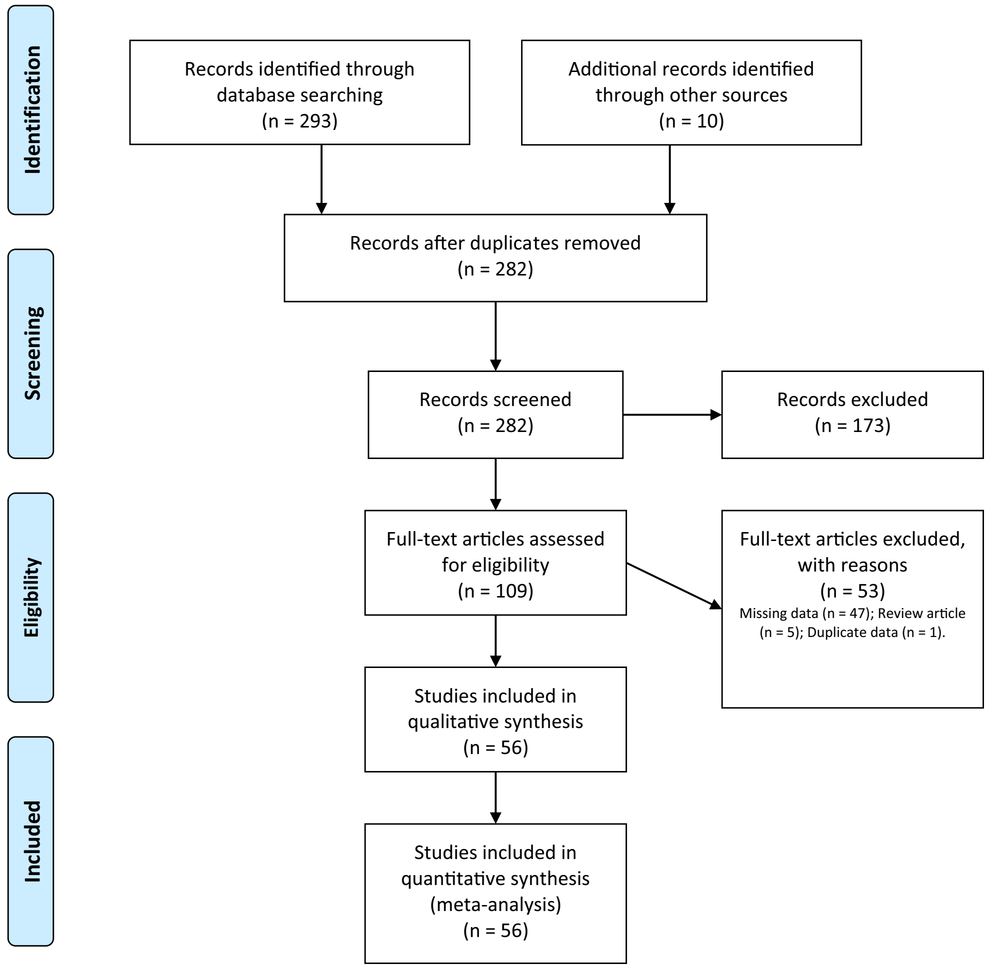


Fig. 1 Flow chart of the literature search. From 282 initially retrieved articles, 56 were analyzed

used other sequences. Detailed characteristics of the analyzed studies are presented in Table 1.

ECV estimate and risk of publication bias

In all studies, ECV was measured by placing one to three regions of interest on the short-axis view, mostly at the mid-ventricular level. Rarely, measurements were repeated on the four-chamber or long-axis view. ECV obtained in different regions of interest was averaged. In all studies, ECV was estimated by using the formula proposed by Arheden et al [90] and validated by Flett et al [11].

As shown in the forest plot of Fig. 2, study-level ECV ranged from 20.2 to 28.5%, showing a high heterogeneity ($Q = 771$, degree of freedom 63, $\tau = 2.0972$, $I^2 = 92\%$, $p < 0.001$); SD ranged from 0.9% [42, 80] to 5.8% [43]. Using the random-effect model, the pooled ECV was 25.6% (95% CI 25.2–26.0%), while the pooled SD was 3.0%, giving an estimated interval of normal ECV in healthy subjects from 19.6 to 31.6%.

At visual inspection, the funnel plot in Fig. S1 (online material) did not show risk of publication bias, as confirmed by the Egger test ($p = 0.728$).

Meta-regression analysis

Meta-regression analysis showed a slight but significant positive correlation between ECV and subjects' age ($\beta = 0.03\%$ per year of age, $p = 0.038$). This test remained significant after correction for multiple testing. A nearly significant negative correlation was found between ECV and the percentage of males ($\beta = -0.02\%$ per unit increase in the percentage of male, $p = 0.053$).

All other meta-regression analyses did not show any significant impact on ECV of the year of publication ($p = 0.159$), acquisition time after contrast agent injection ($p = 0.093$), time of repetition ($p = 0.556$), time of echo ($p = 0.644$), body mass index ($p = 0.692$), left ventricular ejection fraction ($p = 0.933$), and contrast agent dose ($p = 0.569$).

Subject age and percentage of males were entered into the multivariate meta-regression analysis, whose results are

Table 1 Main characteristics of the 56 analyzed articles

Study	N	Male (%)	Age* (years)	BMI* (kg/m^2)	LVEF* (%)	MFS (T)	Sequence	TE (ms)	TR (ms)	GBCA†	GBCA dose* (mmol/kg)	Timing‡* (min)	Native T1 (ms)*	Post-contrast T1 (ms)*	Hematocrit* (%)	ECV* (%)
Mordi et al 2017 [36]	28	50	68	26	64	3	MOLLI					15	1194 ± 29			27.0 ± 4.3
Storz et al 2017 [31]	218	50	54	27	69	3	MOLLI	1.1		4	0.2	10	1202 ± 46			24.6 ± 2.8
Wang et al 2017 [37]	97	71	50	23	58	1.5	MOLLI	1.0	2.5	4	0.2	15				26.9 ± 2.7
Youn et al 2017 [38]	19	65	54		66	3	MOLLI	1.0	2.4	2	0.2	15	1214 ± 37		43.0	25.8 ± 2.2
Altabella et al 2016 [39]	8					1.5	MOLLI	1.1	2.6	1	0.1	15	1012 ± 48	461 ± 33		24.5 ± 2.5
Boentert et al 2016 [40]	18	67	44	24	61	1.5	MOLLI	1.1		4	0.15	20				25.4 ± 2.5
Bulluck et al 2016 [41]	20	90	60		63	1.5	MOLLI	1.1		5	0.1	15				26.4 ± 2.1
Hanneman et al 2016 [42]	10	50	32		60	1.5	MOLLI			2	0.2	10	1006 ± 35	374 ± 22	41.0	27.0 ± 3.1
Lee et al 2016 [43]	7	57	56	23	67	3	MOLLI	1.0	2.4	2	0.2	15			43.4	26.3 ± 0.9
Luetkens et al 2016 [44]	22	68	45	25	65	3	MOLLI			2	0.2	10	1087 ± 55	396 ± 64		26.5 ± 3.7
Luetkens et al 2016 [44]	22	68	45	25	65	3	MOLLI			2	0.2	20	1087 ± 55	440 ± 67		26.1 ± 2.8
Luetkens et al 2016 [45]	50	60	39	25	61	1.5	MOLLI			2	0.2	11	967 ± 28		40.7	27.7 ± 5.8
Luetkens et al 2016 [45]	50	60	39	25	61	1.5	ShMOLLI			2	0.2	11	831 ± 27		40.7	25.3 ± 4.5
Mayr et al 2016 [46]	20				66	1.5	MOLLI	1.0	2.4	4	0.15	20	962 (947–987)	526 (508–553)		25.0 ± 1.5
Mordi et al 2016 [47]	21		48		65	1.5	MOLLI	1.1		2	0.15	10	952 ± 31			26.2 ± 2.9
Olivieri et al 2016 [48]	16		16		60	1.5	MOLLI	1.1	2.6	2	0.15	15	984			25.2 ± 3.4
Olivieri et al 2016 [48]	16		16		60	1.5	SASHA	1.1	2.6	2	0.15	22	1134			20.7 ± 2.5
Schmacht et al 2016 [49]	17	29	54	24	65	1.5	MOLLI	1.1		5	0.2	15	992 ± 28	435 ± 26		26.4 ± 3.0
Soslow et al 2016 [50]	11	100	25	23	60	1.5	MOLLI	1.1	2.6	4	0.2	15	988 ± 14			24.0 ± 1.0
Weingärtner et al 2016 [51]	20	50	27			3	MOLLI	1.0	2.6	5	0.2	15	1183 ± 36	541 ± 34		26.0 ± 2.6
Weingärtner et al 2016 [51]	20	50	27			3	SAPPHIRE	1.0	2.6	5	0.2	15	1578 ± 36	746 ± 50		20.2 ± 2.0
Weingärtner et al 2016 [51]	20	50	27			3	SASHA	1.0	2.6	5	0.2	15	1523 ± 41	722 ± 57		21.3 ± 2.5
Zhao et al 2016 [52]	13	10	53	26	63	3	MOLLI	1.0	2.6	4	0.1	15	1248 ± 32	545 ± 53		25.1 ± 1.6
aus dem Siepen et al 2015 [53]	56	66	52		62	1.5	MOLLI	1.8	3.5	4	0.2	10	1020 ± 40	442 ± 43	42.0	23.0 ± 3.0
Banypersad et al 2015 [54]	54	46	46		67	1.5	ShMOLLI	4.6	9.8	5	0.1	15				25.0 ± 2.0
Barison et al 2015 [55]	10	0	48		66	1.5	Mcine-IR GE	2.8	6.0	3	0.2	15	811 ± 89	390 ± 36	39.0	28.0 ± 4.0
Barison et al 2015 [56]	15	73	52		67	1.5	Mcine-IR GE	2.8	6.0	5	0.2	15				25.0 ± 4.0
Barison et al 2015 [57]	30	70	39		65	1.5	Mcine-IR GE	2.8	6.0	3	0.2	15				26.0 ± 4.0
Edwards et al 2015 [58]	43	56	57	26	73	1.5	MOLLI	1.0	2.4	4	0.15	15	955 ± 30	497 ± 37	41.0	25.0 ± 3.0
Edwards et al 2015 [59]	26	65	27	25	68	1.5	MOLLI			2	0.15	15				25.0 ± 1.0
Ertel et al 2015 [60]	30	47	52	28	64	1.5	MOLLI	1.1	2.7	4	0.15	15	971 ± 41		40.0	26.0 ± 2.4
Hong et al 2015 [61]	10	70	54		65	3	MOLLI	1.0	2.4	2	0.2	15	1206 ± 37		42.5	25.6 ± 3.2
Kuruvilla et al 2015 [62]	22	68	54			1.5	MOLLI	1.1	2.5	4	0.15	15	967 ± 35	503 ± 35		26.0 ± 2.0
Mehta et al 2015 [63]	10	20	24	24	61	1.5	ShMOLLI	1.2	2.7	4	0.15	25	971 (948–986)	519 (491–546)		27.1 ± 1.4
Ntusi et al 2015 [64]	39	28	49	24	73	1.5	ShMOLLI	1.1		5	0.15	15	961 ± 18	468 ± 32	42.0	27.9 ± 2.0
Singh et al 2015 [65]	22	68	68		59	3	MOLLI			2	0.15	20	1092 ± 34		43.0	25.1 ± 3.0
Brouwer et al 2014 [66]	14	57	48			1.5	MOLLI			4	0.2	15			42.0	26.0 ± 2.0
Chin et al 2014 [67]	20	50	55			3	MOLLI			2	0.1	15	1180 ± 28	672 ± 56		26.0 ± 1.6
Dabir et al 2014 [68]	34	52	41			1.5	MOLLI	1.6	3.3	2	0.15	18	950 ± 21	415 ± 113	40.0	25.0 ± 4.0
Dabir et al 2014 [68]	32	52	41			3	MOLLI	1.6	3.3	2	0.15	18	1052 ± 23	421 ± 131	40.0	26.0 ± 4.0
Edwards et al 2014 [69]	35	63	59	26	74	1.5	MOLLI			2	0.15	15	939 ± 93	467 ± 89		25.0 ± 2.0
Florian et al 2014 [70]	17	100	33		65	1.5	MOLLI	1.1		4	0.15	20			44.0	24.0 ± 2.0
Luetkens et al 2014 [71]	42	64	39	25	63	3	MOLLI			2	0.2	10	1089 ± 45		40.8	23.6 ± 4.1
Neilan et al 2014 [72]	8	14	63	26	61	3	Look-Locker			4	0.15	25			45.0	27.0 ± 2.5

Table 1 (continued)

Study	*N*	Male (%)	Age* (years)	BMI* (kg/m²)	LVEF* (%)	MFS (T)	Sequence	TE (ms)	TR (ms)	GBCA†	GBCA dose* (mmol/kg)	Timing‡* (min)	Native T1 (ms)*	Post-contrast T1 (ms)*	Hematocrit* (%)	ECV* (%)
Radunski et al 2014 [73]	21	81	34	25	59	1.5	MOLLI	1.1	2.6	1	0.075	15	1051 (1010–1063)	579 (544–608)		25.0 ± 1.5
Thuny et al 2014 [74]	16		50		64	1.5	MOLLI			5	0.2	5				26.8 ± 1.8
Brooks et al 2013 [75]	8		51			1.5	MOLLI	1.1	2.5	4	0.15	20	963 ± 42	544 ± 36	37.0	26.8 ± 2.0
Neilan et al 2013 [76]	15	47	56			3	MOLLI			4	0.15	30			42.0	28.0 ± 2.0
Neilan et al 2013 [77]	32	44	49	26	64	3	MOLLI	2.5	5.5	4	0.15	30				28.0 ± 3.0
Puntmann et al 2013 [78]	21	31	38	24	61	3	MOLLI	1.6	3.3	2	0.2	15	1056 ± 27	454 ± 53		26.0 ± 5.0
Puntmann et al 2013 [79]	30	63	43	24	63	3	MOLLI	1.6	3.3	2	0.2	10	1070 ± 55	402 ± 58	44.0	27.0 ± 1.0
Salerno et al 2013 [80]	7		34			1.5	MOLLI	1.1	2.5	4	0.1	48	974 ± 23	606 ± 31		28.5 ± 1.8
Shah et al 2013 [81]	12	58	15	20	59	3	Look-Locker	2.2	5.0	4	0.15	30				26.4 ± 0.9
Thompson et al 2013 [82]	23	48	42	24	64	1.5	SASHA	1.4	2.8	4	0.15	15	1177 ± 27	559 ± 51	42.0	22.2 ± 3.1
Fontana et al 2012 [17]	50	53	47			1.5	ShMOLLI			5	0.1	45				27.0 ± 3.0
Kawel et al 2012 [83]	23	33	28			3	MOLLI	1.0	2.4	1	0.1	12	1286 ± 59	555 ± 33	40.0	27.0 ± 3.0
Kawel et al 2012 [83]	23	36	28			1.5	MOLLI	1.1	2.7	4	0.15	12	1003 ± 46	522 ± 34	41.0	28.0 ± 3.0
Kawel et al 2012 [83]	23	31	28			3	MOLLI	1.0	2.4	4	0.15	12	1286 ± 59	538 ± 34	40.0	28.0 ± 3.0
Kellman et al 2012 [84]	62	48	44	27	62	1.5	MOLLI	1.0	2.4	4	0.15	15	965 ± 35			25.4 ± 2.5
Mongeon et al 2012 [85]	9	33	45		69		Look-Locker			4	0.15	15			41.0	24.0 ± 2.0
Sado et al 2012 [86]	81	52	44	26	67	1.5	FLASH	1.0		5	0.1	45			42.0	25.3 ± 3.5
Ugander et al 2012 [87]	60	52	49	26	62	1.5	MOLLI	1.0	2.5	4	0.15	15				27.0 ± 3.0
Broberg et al 2010 [88]	14	57	38		66		Look-Locker			4	0.15	15				24.8 ± 2.0
Jerosch-Herold et al 2008 [89]	9	64	45		69	3	Look-Locker	1.7	3.4	4	0.03	10			41.0	24.0 ± 3.0

BMI, body mass index; *LVEF*, left ventricular ejection fraction; *MFS*, magnetic field strength; *TE*, time of echo; *TR*, time of repetition; *GBCA*, gadolinium-based contrast agent; *MOLLI*, modified Look-Locker inversion recovery; *ShMOLLI*, shortened MOLLI; *SASHA*, saturation recovery single-shot acquisition; *FLASH*, fast low-angle single shot; *Mcine-IR*, modified-cine inversion recovery

*Mean and standard deviation or median and interquartile range. † 1, gadobenate dimeglumine; 2, gadobutrol; 3, gadodiamide; 4, gadopentetate dimeglumine; 5, gadoterate meglumine. ‡ Time of acquisition after contrast agent administration shown in Table 2. Although both the two above-mentioned variables lost statistical significance at multivariate analysis, an inference could be made, so that a virtual sample of only 50-year-old females would result in a mean ECV of 26.9%, while a sample of only 50-year-old men would result in a mean ECV of 24.9%. As sex was a continuous variable in this meta-analysis (percentage of male in the analyzed studies), we could not provide separate reference normality intervals for male and female.

Subgroup analysis

Subgroup analysis did not show any impact on ECV of neither the magnetic field strength ($p = 0.896$; Fig. S2) nor the type of contrast agent ($p = 0.759$; Fig. S3).

A significant impact on ECV of the sequence used for acquisition was found ($p = 0.003$), even after correction for multiple testing. Heterogeneity was lower but still high, with I^2 of 82% for studies using ShMOLLI and 87% for studies using MOLLI ($p < 0.001$) (Fig. S4). The pooled ECV from studies using MOLLI was 25.9% (95% CI 25.5–26.4%), with a pooled SD of 3.0%, for a reference interval of 19.9–31.9%. The pooled ECV from studies using ShMOLLI was 26.9% (95% CI 25.5–28.3%), with a pooled SD of 3.3%, for a reference interval of 20.3–33.5%.

Quality appraisal

Data of the quality appraisal of the analyzed studies is displayed in Table 2. Among the 56 analyzed studies, 10 (18%) studies were of high quality, 38 (68%) were of moderate quality, and 8 (14%) were of low quality.

Discussion

Our systematic review with meta-analysis included 56 articles providing MRI-derived myocardial ECV in healthy subjects, published from July 2008 [89] to June 2018 [36] (some recent articles were available as "e-pub ahead of print" at the search time). The pooled MRI-derived ECV obtained on the basis of 1851 healthy subjects was 25.6% (95% CI 25.2–26.0%). From the pooled SD, we obtained a reference normality interval from 19.6 to 31.6%, to be considered as a reference for comparison in patients with diseases implying an increase or reduction in ECV.

Although the statistical heterogeneity was very high (I^2 = 92%), the ECV estimate resulted to be quite robust, with low variation among studies. In fact, excluding two outliers of 20.2% [51] and 20.7% [48], ECV ranged from 23.0 [53] to 28.5% [80]. Of note, these two outliers were obtained using the SAPPHIRE [51] and SASHA [48] sequences, which were used only by those authors. Indeed, Roujol et al [91] have already demonstrated that these two sequences yield lower ECV values and have lower precision. The apparent paradox of a robust ECV accompanied by high heterogeneity may be partially explained as a statistical issue, as I^2 reflects the degree of overlap of 95% CIs across studies. In fact, from the forest plot in Fig. 2, it is clear that 95% CIs of the studies by Olivieri et al [48] and Weingärtner et al [51] do not overlap with that of the study by Salerno et al [80]. This separation highly contributed to the heterogeneity.

Notably, the pooled ECV obtained in this meta-analysis (25.6%) was from slightly to substantially lower than that observed in several ischemic and non-ischemic myocardial diseases. For example, patients with dilated cardiomyopathy with negative LGE showed an ECV of 30.7% ± 5.9% (mean ± SD) [61]. The same reasoning holds for patients with myocarditis, in whom a median ECV of 31% (interquartile range 28–34%) has been reported [73]. Higher ECV may be observed in patients with chronic myocardial infarction, with a mean value of 53% ± 10% [92], or with amyloidosis, with a mean ECV reported to be 47% ± 7% [86].

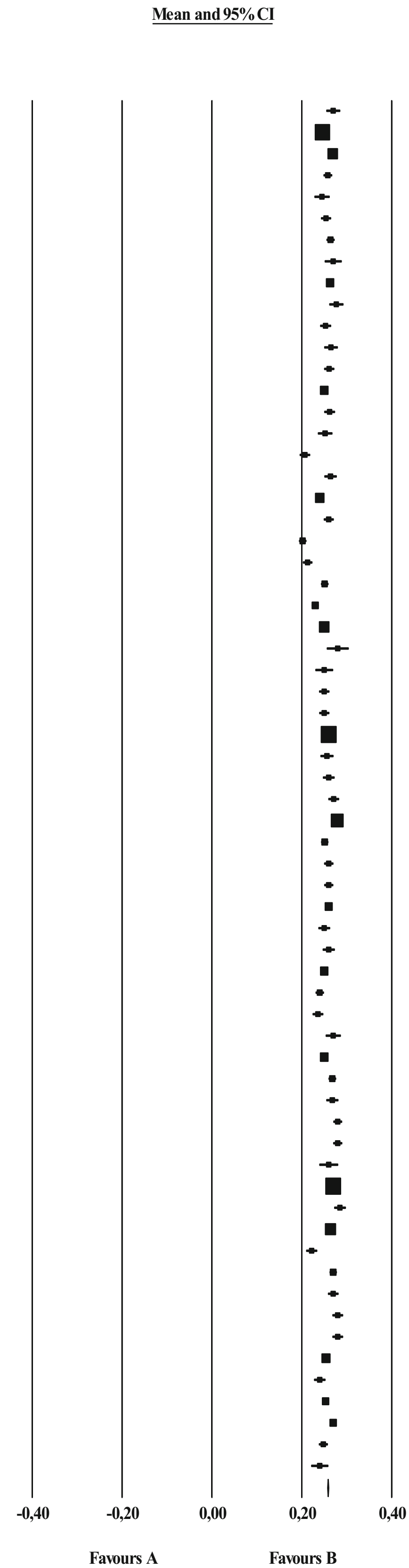
The modeled normality intervals we obtained deserve a particular comment. Subjects with an ECV out of these intervals (from 19.9 to 31.9% for MOLLI sequences; from 20.3 to 33.5% for ShMOLLI sequences) should be considered as affected with an abnormal myocardial condition, although normal values may be still found in case of initial or mild myocardial involvement or not changed at all, as is for rheumatoid arthritis, iron overload, and Anderson-Fabry disease [93]. Indeed, the reference normality intervals we provided are quite large and are overlapped with ECV values reported for patients with dilated cardiomyopathy but negative LGE [61] or with myocarditis [73].

Notably, the width of our reference interval is influenced by the high data heterogeneity that, in turn, depends on the impact on ECV of patient age and sex. Our data are collections of males and females with variable age so that we cannot provide separate reference intervals considering age and sex, thus limiting their clinical application. This is an intrinsic limitation of study-level meta-analyses and only a large population study can provide accurate reference normality intervals of males and females. However, such a study would raise ethical issues due to the intravenous administration of a gadolinium-based contrast agent. A good alternative could be patient-level meta-analysis, for which data sharing from the authors of the individual studies is necessary [94].

Few weeks before the submission of this study, another meta-analysis on the same topic was published by Gottbrecht et al [95]. They evaluated a larger sample of studies for a total of 5541 participants, as they used a larger definition of healthy subjects, including those free of any known heart disease or overt symptoms of heart disease, and those free of any findings of myocardial scar on cardiac MRI. These might perhaps include patients with cardiomyopathies with negative

Fig. 2 Forest plot of the 56 analyzed studies, for a total of 64 independent study parts. Heterogeneity among studies was very high ($I^2 = 92\%$). The last row shows the pooled extracellular volume obtained using the random-effect model

Model	Study name	Statistics for each study		
		Mean	Lower limit	Upper limit
	Mordi 2017	0,270	0,254	0,286
	Storz 2017	0,246	0,242	0,250
	Wang 2017	0,269	0,264	0,274
	Youn 2017	0,258	0,248	0,268
	Altabella 2016	0,245	0,228	0,262
	Boentert 2016	0,254	0,242	0,266
	Bulluck 2016	0,264	0,255	0,273
	Hanneman 2016	0,270	0,251	0,289
	Lee 2016	0,263	0,256	0,270
	Luetkens 2016 (1a)	0,277	0,261	0,293
	Luetkens 2016 (1b)	0,253	0,241	0,265
	Luetkens 2016 (2a)	0,265	0,250	0,280
	Luetkens 2016 (2b)	0,261	0,249	0,273
	Mayr 2016	0,250	0,243	0,257
	Mori 2016	0,262	0,250	0,274
	Olivieri 2016 (a)	0,252	0,235	0,269
	Olivieri 2016 (b)	0,207	0,195	0,219
	Schmacht 2016	0,264	0,250	0,278
	Soslow 2016	0,240	0,234	0,246
	Weingartner 2016 (a)	0,260	0,249	0,271
	Weingartner 2016 (b)	0,202	0,193	0,211
	Weingartner 2016 (c)	0,213	0,202	0,224
	Zhao 2016	0,251	0,242	0,260
	aus dem Siepen 2015	0,230	0,222	0,238
	Banypersad 2015	0,250	0,245	0,255
	Barison 2015 (1)	0,280	0,255	0,305
	Barison 2015 (2)	0,250	0,230	0,270
	Edwards 2015 (1)	0,250	0,238	0,262
	Edwards 2015 (2)	0,250	0,238	0,262
	Ertel 2015	0,260	0,256	0,264
	Hong 2015	0,256	0,241	0,271
	Kuruvilla 2015	0,260	0,247	0,273
	Mehta 2015	0,271	0,259	0,283
	Ntusi 2015	0,279	0,275	0,283
	Singh 2015	0,251	0,243	0,259
	Barison 2014	0,260	0,249	0,271
	Brower 2014	0,260	0,250	0,270
	Chin 2014	0,260	0,253	0,267
	Dabir 2014 (a)	0,250	0,237	0,263
	Dabir 2014 (b)	0,260	0,246	0,274
	Edwards 2014	0,250	0,243	0,257
	Florian 2014	0,240	0,230	0,250
	Luetkens 2014	0,236	0,224	0,248
	Neilan 2014	0,270	0,253	0,287
	Radunski 2014	0,250	0,244	0,256
	Thuny 2014	0,268	0,259	0,277
	Brooks 2013	0,268	0,254	0,282
	Neilan 2013 (1)	0,280	0,270	0,290
	Neilan 2013 (2)	0,280	0,270	0,290
	Puntmann 2013 (1)	0,260	0,239	0,281
	Puntmann 2013 (2)	0,270	0,266	0,274
	Salerno 2013	0,285	0,272	0,298
	Shah 2013	0,264	0,259	0,269
	Thompson 2013	0,222	0,209	0,235
	Fontana 2012	0,270	0,262	0,278
	Kawel 2012 (a)	0,270	0,258	0,282
	Kawel 2012 (b)	0,280	0,268	0,292
	Kawel 2012 (c)	0,280	0,268	0,292
	Kellman 2012	0,254	0,248	0,260
	Mongeon 2012	0,240	0,227	0,253
	Sado 2012	0,253	0,245	0,261
	Ugander 2012	0,270	0,262	0,278
	Broberg 2010	0,248	0,238	0,258
	Jerosch-Herold 2008	0,240	0,220	0,260
Fixed		0,257	0,256	0,258



Meta Analysis

Table 2 Results of the quality appraisal of the analyzed studies using the Newcastle-Ottawa scale

Study	Selection				Comparability		Exposure			Total	Quality
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9		
Mordi et al 2017 [36]	1	1	1	1	1	0	1	1	0	7	High
Storz et al 2017 [31]	1	1	0	1	1	0	1	1	0	6	Moderate
Wang et al 2017 [37]	1	1	0	0	1	0	1	1	0	5	Moderate
Youn et al 2017 [38]	1	1	0	0	1	0	1	1	0	5	Moderate
Altabella et al 2016 [39]	0	1	0	0	0	0	0	1	0	2	Low
Boentert et al 2016 [40]	1	0	1	0	1	0	1	1	0	5	Moderate
Bulluck et al 2016 [41]	1	0	0	1	1	0	1	1	0	5	Moderate
Hanneman et al 2016 [42]	1	1	1	1	1	1	1	1	0	8	High
Lee et al 2016 [43]	1	0	1	1	1	0	1	1	0	6	Moderate
Luetkens et al 2016 [44]	0	0	0	1	1	0	0	1	0	3	Low
Luetkens et al 2016 [45]	1	0	0	1	1	0	1	1	0	5	Moderate
Mayr et al 2016 [46]	0	1	1	1	1	0	0	0	0	4	Moderate
Mordi et al 2016 [47]	1	0	0	1	1	0	1	1	0	5	Moderate
Olivieri et al 2016 [48]	0	0	0	1	1	0	0	1	0	3	Low
Schmacht et al 2016 [49]	1	0	0	1	1	0	1	1	0	5	Moderate
Soslow et al 2016 [50]	1	0	0	1	1	0	1	1	0	5	Moderate
Weingärtner et al 2016 [51]	1	0	0	0	0	0	1	0	0	2	Low
Zhao et al 2016 [52]	0	0	1	1	1	0	0	1	0	4	Moderate
aus dem Siepen et al 2015 [53]	1	1	0	1	1	0	1	1	0	6	Moderate
Banypersad et al 2015 [54]	1	1	0	0	1	0	1	1	0	5	Moderate
Barison et al 2015 [55]	1	1	1	1	1	0	0	1	0	6	Moderate
Barison et al 2015 [56]	1	0	1	1	1	0	1	1	0	6	Moderate
Barison et al 2015 [57]	1	0	0	1	1	0	1	1	0	5	Moderate
Edwards et al 2015 [58]	1	0	0	1	1	0	1	1	0	5	Moderate
Edwards et al 2015 [59]	1	1	0	1	1	0	1	1	0	6	Moderate
Ertel et al 2015 [60]	1	0	0	1	1	0	1	1	0	5	Moderate
Hong et al 2015 [61]	1	1	1	1	1	0	1	1	0	7	High
Kuruvilla et al 2015 [62]	1	0	1	1	1	0	1	1	0	6	Moderate
Mehta et al 2015 [63]	0	0	1	1	1	0	0	1	0	4	Moderate
Ntusi et al 2015 [64]	1	1	1	1	1	0	1	1	0	7	High
Singh et al 2015 [65]	1	0	1	1	1	0	1	1	0	6	Moderate
Brouwer et al 2014 [66]	1	0	0	1	1	0	1	1	0	5	Moderate
Chin et al 2014 [67]	0	0	1	1	1	0	0	1	0	4	Moderate
Dabir et al 2014 [68]	0	0	1	1	0	1	0	0	0	3	Low
Edwards et al 2014 [69]	1	1	1	1	1	0	1	1	0	7	High
Florian et al 2014 [70]	1	0	0	1	1	0	1	1	0	5	Moderate
Luetkens et al 2014 [71]	1	0	0	1	1	0	1	1	0	5	Moderate
Neilan et al 2014 [72]	1	0	1	1	1	0	1	1	0	6	Moderate
Radunski et al 2014 [73]	1	1	1	1	1	0	1	1	0	7	High
Thuny et al 2014 [74]	1	1	1	1	1	0	1	1	0	7	High
Brooks et al 2013 [75]	1	1	0	1	1	0	1	1	0	6	Moderate
Neilan et al 2013 [76]	1	0	0	1	1	0	1	1	0	5	Moderate
Neilan et al 2013 [77]	1	0	0	0	0	0	1	0	0	2	Low
Puntmann et al 2013 [78]	1	0	1	1	1	0	1	1	0	6	Moderate
Puntmann et al 2013 [79]	1	1	1	1	1	0	1	1	0	7	High
Salerno et al 2013 [80]	0	0	1	1	0	1	0	0	0	3	Low
Shah et al 2013 [81]	1	0	0	1	1	0	1	1	0	5	Moderate

Table 2 (continued)

Study	Selection				Comparability		Exposure			Total	Quality
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9		
Thompson et al 2013 [82]	1	0	0	1	1	0	1	1	0	5	Moderate
Fontana et al 2012 [17]	1	1	1	1	1	0	1	1	0	7	High
Kawel et al 2012 [83]	0	0	1	1	0	1	0	0	0	3	Low
Kellman et al 2012 [84]	1	1	1	1	1	0	1	1	0	7	High
Mongeon et al 2012 [85]	1	1	0	1	1	0	1	1	0	6	Moderate
Sado et al 2012 [86]	1	0	1	1	1	0	1	1	0	6	Moderate
Ugander et al 2012 [87]	0	0	1	1	1	0	0	1	0	4	Moderate
Broberg et al 2010 [88]	1	1	0	1	1	0	1	1	0	6	Moderate
Jerosch-Herold et al 2008 [89]	1	0	0	1	1	0	1	1	0	5	Moderate

LGE. Moreover, they only presented an estimate of the pooled ECV without reference normality intervals. Our pooled ECV (25.6%) was slightly lower than that obtained by them (25.9%) that is in line with the different inclusion criteria.

Notably, the contraindication to the intravenous administration of gadolinium-based contrast agents in patients with renal failure may prevent the calculation of ECV. In these cases, the assessment of native T1 can be a valid alternative [96]. The clinical applications of myocardial T1 mapping and ECV were recently discussed by Kim et al [93] for the main clinical settings, including the reduction in native T1 for iron overload and Anderson-Fabry disease, and for the reduction of both T1 and ECV in lipomatous metaplasia and fat accumulation.

We should underline that the calculation of ECV was based on the hematocrit in all the studies we analyzed. This could be considered as a general limitation of the MRI-derived ECV technique, as it may be not available in some cases. Treibel et al [97] proposed the use of a synthetic hematocrit, based on the relationship with blood native T1, as a surrogate of the laboratory value. Robinson et al [98] recently demonstrated that there is no significant difference between myocardial ECV obtained using synthetic hematocrit and that obtained using the standard method at 1.5 T. However, there is still no agreement on the clinical use of the synthetic hematocrit; so, we excluded the papers using it from our analysis.

Importantly for clinical practice, subgroup analysis found a significant impact on ECV of the sequence used for T1 mapping. In particular, the MOLLI sequence, which was the most used across studies, was associated with a lower ECV (25.9%) than the ShMOLLI sequence (26.9%). Other sequences, including the original Look-Locker sequence, yielded an even lower value (24.2%). On the other hand, Roujol et al [91] previously demonstrated that all the studied sequences have variable accuracy and reproducibility. As MOLLI and ShMOLLI sequences are currently mostly used, the reference ranges for normal myocardial ECV should be differentiated for the sequence under consideration: from 19.9 to 31.9% for MOLLI and from 20.3 to 33.5% for ShMOLLI. Again, these large intervals reflect the inclusion of variable samples of males and females of variable age. Notably, we used subgroup analysis instead of meta-regression analysis for categorical variables. In general, subgroup and meta-regression analyses provide equivalent results, although with different ways of presentation and degrees of interpretability. For each categorical variable, we could provide a pooled ECV as well as a normality interval in each subgroup. Instead, with meta-regression, we would have chosen a reference value and would have presented results in terms of change versus the reference value. Moreover, we would have not able to calculate a normality interval. In our opinion, this would be less informative compared with data presented using subgroup analysis.

Although meta-regression analysis showed no impact of the acquisition time after contrast agent injection or of any other technical parameter, a standardization of the acquisition protocol is needed for a robust use in clinical practice. A consensus statement by the Society for Cardiovascular Magnetic Resonance endorsed by the European Association for Cardiovascular Imaging [99] recommends that, for ECV measurements, post-contrast T1 mapping should be performed from 10 to 30 min after contrast agent administration. A narrower time interval could make the ECV estimate more reproducible.

Our study has limitations. The most important limitation has already been discussed in relation to the intrinsic nature of study-level meta-analyses: the lack of individual patient data prevented from estimating more stratified normality intervals taking into consideration age and sex. A second limitation was the incomplete data independence, as 8 study parts for a total of 206 subjects (11% of the overall sample) were studied twice or three times. However, the low weight of this data dependence should not have influenced the reliability of our results.

In conclusion, considering that the analyzed articles had a moderate-to-high quality without the risk of publication bias, we provided an accurate point estimate of the myocardial ECV in healthy subjects (25.6%), depending on the sequence used, with reference intervals from 19.9 to 31.9% for MOLLI sequence and from 20.3 to 33.5% for ShMOLLI sequence. In the range of observed heart function, ECV seems independent of the left ventricle ejection fraction but slightly increasing with age and decreasing with the percentage of males.

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Compliance with ethical standards

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Informed consent Written informed consent was not required for this study because the article type is a systematic review with meta-analysis.

Ethical approval Institutional Review Board approval was not required because the article type is a systematic review with meta-analysis.

Methodology
• Prospective
• Performed at one institution

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