ORIGINAL ARTICLE

Mismatch between the origin of premature ventricular complexes and the noncompacted myocardium in patients with noncompaction cardiomyopathy patients: involvement of the conduction system?

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Background: Noncompaction cardiomyopathy (NCCM) is considered to be the result of an arrest in the normal myocardial embryogenesis. The histological, developmental, and electrophysiological explanation of ventricular arrhythmias in NCCM is still unknown. The aim of this study was to determine the origin of premature ventricular contractions (PVCs) in NCCM and to identify any predominant arrhythmic foci.

Methods: Retrospective data from our NCCM registry including 101 patients were analyzed. A total number of 2069 electrocardiograms (ECGs) were studied to determine the origin of PVCs. Echocardiographic data were analyzed in patients with PVCs in all 12 leads. Segments affected by noncompaction (NC) were compared with the origin of PVCs.

Results: PVCs were documented in 250 ECGs from 55 (54%) patients. Thirty-five ECGs recorded PVCs on all 12 leads and the origin of 20 types of PVCs could be determined. Ninety-five percent of PVCs did not originate from left ventricular NC myocardial areas and two PVCs (10%) had a true myocardial origin. All other PVCs originated from structures such as the outflow tracts (8/20), the fascicles (7/20), especially the posteromedial fascicle (6/20), and the mitral and tricuspid annulus (3/20).

Conclusions: Our data suggest that PVCs in NCCM mainly originate from the conduction system and related myocardium.

KEYWORDS

cardiac conduction system, noncompaction cardiomyopathy, premature ventricular beats, ventricular arrhythmias

The pathogenesis of noncompaction cardiomyopathy has not been conclusively established. Classically it has been theorized as an arrest in the embryogenic development of the heart, a fault in the compaction of the myocardium. Alternatively it has been proposed that there is an abnormal persistence of the trabecular layer or altered regulation in cell proliferation, differentiation, and maturation during ventricular

wall formation (Chen et al., 2009; Henderson & Anderson, 2009). The diagnosis relies on morphological findings with cardiac imaging, in particular echocardiography and magnetic resonance imaging (Jenni et al., 2001). In humans ventricular noncompaction is usually localized. Even if only a minor proportion of the ventricular wall is affected, diffuse ventricular contractile dynamics can be perturbed (Jenni et al., 2001). The classic presentation of NCCM includes heart failure, thromboembolic events, supraventricular arrhythmias, and

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ventricular arrhythmias resulting in sudden cardiac death (Ichida et al., 1999; Ritter et al., 1997). Until now there is no clear histological, developmental, or electrophysiological evidence for the origin of premature ventricular contractions (PVCs) and ventricular arrhythmias in NCCM. The aim of this study was to determine the origin of PVCs in NCCM and to identify predominant arrhythmic foci and the relation with affected myocardial areas.

1 | METHODS

1.1 | Study population

The screened patient population consisted of 101 patients with NCCM (mean age 48 ± 14 years, 45% male), who were followed from 2005 to 2011 at the outpatient clinic of our tertiary referral center. These NCCM patients strictly fulfilled all four echocardiographic diagnostic Jenni criteria (Jenni et al., 2001): (i) excessively thickened left ventricular (LV) myocardial wall with a two-layered structure comprising a compact epicardial layer and a noncompacted endocardial layer of prominent trabeculations and deep intertrabecular recesses; (ii) maximal end-systolic ratio of the noncompacted/compacted wall >2 measured at the parasternal short axis; (iii) color Doppler evidence of deep perfused intertrabecular recesses in communication with the LV cavity; and (iv) absence of coexisting cardiac anomalies.

1.2 | Demographical data

Demographic and clinical data at the time of PVC occurrence were registered. These data included age, gender, blood pressure, New York Heart Association (NYHA) functional class, known documented mutation, presence of an implantable cardioverter defibrillator (ICD), and the use of any cardiac drugs, including antiarrhythmic drugs.

1.3 | Echocardiography

Two-dimensional echocardiographic images were obtained using a commercially available ultrasound system (iEE, Philips, Best, The Netherlands). Global LV function (GLVF) was visually assessed and classified in four groups: 1 = normal LV function, 2 = mild LV

dysfunction, 3 = moderate LV dysfunction, and 4 = severe LV dysfunction. No measurements of LV volume and ejection fraction were made due to the inherent problem of identifying the endocardial border in the presence of hypertrabeculation. According to recommendations from the American Heart Association on standardized myocardial segmentation and nomenclature for tomographic imaging of the heart, the 17-segment model (Fig. 1) was used for the assessment of regional noncompaction (Cerqueira et al., 2002). A segment was defined as noncompacted if at least 75% of the segment showed noncompaction.

1.4 | Electrocardiography

All ECGs were analyzed by two experienced and independent electrophysiologists who determined the origin of PVCs based on their morphology, upslope, QRS width, transition, and axis (Josephson, 2008). The reviewers were blinded to the echocardiographic evaluation of the ventricles. PVCs were considered monomorphic if only one, and multiform if two or more morphologies were documented in the same patient. If a PVC was captured in all 12 ECG leads it was categorized to one of the following ventricular areas: aortomitral continuity, right and left ventricular outflow tract (RVOT/LVOT), septum, upper septal fascicle (USF), posteromedial fascicle (PMF), anterolateral fascicle (ALF), mitral and tricuspid annulus, septal, and free left or right ventricular wall. Fascicular origin was distinguished from true LV myocardial origin as PMF and ALF have a fast upstroke, smaller QRS between 100 and 140 ms, and a short RS interval (60–80 ms).

1.5 | Statistics

Statistical analysis was performed with IBM SPSS Statistics 21. Descriptive data for continuous variables were presented as mean $\pm$ SD and categorical variables as frequency (%).

2 | RESULTS

2.1 | Patient characteristics and clinical presentation

Within the patient population a total of 2069 ECGs were recorded and analyzed in the 101 NCCM cases. PVCs were seen on 250 ECGs in

FIGURE 1 Prevalence of noncompaction in a 17-segment LV model in each patient ($n = 16$). In black the number of each segment according to the recommendations of the American Heart Association (C1) is presented. The red number represents the number of noncompacted segments in all 16 patients. LA, left atrium, LV, left ventricle

FIGURE 2 Flowchart on the selection of patients included in this study

TABLE 1 Clinical patient characteristics—descriptive data presented with percentages in parenthesis

Clinical variable	Patients with PVCs in all 12 leads (n = 16)
Age at time of PVC occurrence, year ^a	42.4 (23–80)
Polymorphic PVC	10/16 (63%)
Monomorphic PVC	6/16 (38%)
Male	7 (44%)
ICD implantation	13 (81%)
Pathogenic mutation	6/16 (3x MYH7m, 1x LMNA/Cm, 1x TNNI3m, 1x PLNm)
LV function, %	
Normal	2/16 (13%)
Mild dysfunction	3/16 (19%)
Moderate dysfunction	3/16 (19%)
Severe dysfunction	8/16 (50%)
Clinical presentation	
Aborted sudden cardiac arrest	2/16 (13%)
Syncope	2/16 (13%)
Spontaneous VT/VF	10/16 (63%)
Heart failure	7/16 (44%)
TIA/CVA	3/16 (19%)
NYHA	
Class I	9/16 (56%)
Class II	4/16 (25%)
Class III	3/16 (19%)
Class IV	0/16 (0%)
Arterial hypertension	1/16 (6%)
Diabetes mellitus	0/16 (0%)
β-blockers	16/16 (100%)
AAD	8/16 (50%)
ACE-I	16/16 (100%)

AAD, antiarrhythmic drugs; ACE-I, angiotensin-converting enzyme inhibitor; ICD, implantable cardioverter defibrillator; LV, left ventricle; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

^aMedian with range in brackets.

54% of patients (55/101) with NCCM. In the remaining 46% (46/101) of patients no PVCs was recorded.

Twenty-nine percent (16/55) of patients had monomorphic and 71% (39/55) had multiform PVCs. In a subgroup of 16 patients (mean age 42.4 ± 17.8 years at time of PVC occurrence, seven men), a total of 35 ECGs could be recorded with PVCs in all 12 leads (Fig. 2). Baseline characteristics of these 16 patients are listed in Table 1.

2.2 | Echocardiographic analysis

Segmental myocardial analysis in a 17-segment LV model in each patient ($n = 16$) has been presented in Fig. 1 and Table 3. Fifty-eight percent (157/272) of the segments showed noncompaction (NC), especially at apical segments (segments 13–17). Ninety-three percent (74/80) of the apical segments were affected, compared to only 36% (13/36) of all basal segments (segments 1–6).

2.3 | ECG analysis

Of the 35 ECGs in which 12-lead PVCs were recorded, the origin of 20 different PVCs could be determined (Josephson, 2008). Thirty percent (6/20) originated from the PMF, 4/20 (20%) from the LVOT, 4/20 (20%) from the RVOT, 2/20 (10%) from the tricuspid annulus, 1/20 (5%) from the USF, 1/20 (5%) from the mitral annulus, 1/20 (5%) from the right ventricular (RV) septum, and 1/20 (5%) from the free RV wall (Fig. 3). All PVC characteristics are shown in Table 2. Ninety-five percent of these PVCs did not originate from LV regions affected by non-compaction (Table 3, Fig. 4). One (5%) PVC possibly originated from a mid-septal noncompacted segment, although the PVC characteristics suggest a more RV-sided septal origin (Tables 2 and 3). In addition, no correlation could be found between the occurrence of a previous spontaneous nonsustained ventricular tachycardia and the location of PVCs.

FIGURE 3 Illustrations of different types of PVCs recorded from NCCM patients. LVOT, left ventricular outflow tract; MA, mitral annulus; PMF, posteromedial fascicle; RVOT, right ventricular outflow tract; RVs, RV septum; TA, tricuspid annulus; USF, upper septal fascicle

3 | DISCUSSION

The major finding of our study is that 95% of analyzed PVCs in NCCM patients do not originate from LV myocardial areas affected by noncompaction (Table 2, Fig. 4). Only two PVCs (10%) had a true myocardial origin, this being the free RV myocardial wall and the myocardial septum. All other PVCs originated from regions such as the outflow tracts, the fascicles (USF, PMF, ALF), and the mitral and tricuspid annulus (Fig. 3). Based on current literature, all of these structures develop out of the primary cardiac conduction system (CCS) (Gourdie et al., 2003; Hucker et al., 2008; Inoue & Becker, 1998; Jongbloed et al., 2008; Katritsis & Becker, 2007; Kurosawa & Becker, 1985; McGuire et al., 1994, 1996; Poelmann et al., 2004; Szili-Torok, van Malderen, & de Groot, 2012;

Wenink, 1976). This gives rise to the hypothesis that the PVCs in NCCM are not causally related to the noncompacted myocardium itself. As NCCM is considered to be the result of an arrest in normal embryogenesis of the myocardium (Engberding & Bender, 1984), we hypothesize that a simultaneous inappropriate development of the primary CCS could result in a more pronounced occurrence of arrhythmias. Former theories about ventricular arrhythmias in NCCM involve microreentry in the trabeculated myocardium, epicardial coronary hypoperfusion, and concurrent developmental arrest of the conduction system (Engberding & Bender, 1984). The latter of these theories seems to be more supported by the findings of this study. Unfortunately, due to a limited study population with different origins of PVCs, no statistically significant correlation could be demonstrated between the origin of PVCs and the occurrence of a previous spontaneous VT (Table 3). Upon further interpreting our data and reviewing the literature, a reentry mechanism seems less likely as EP testing could not induce VT in the majority of the patients in one study (Kobza et al., 2008).

3.1 | Embryonic remnants and inappropriate purkinje fiber/fascicle formation

Working myocardium and conduction cells appear to be derived from a common myogenic precursor in the embryonic tubular heart, i.e., a bipotential myocardial cell population that is selectively recruited to the developing cardiac pace making and conduction system (Gourdie et al., 2003). The “multiple ring” model has been postulated for the formation of the cardiac conduction system. It states that after looping of the heart has started, four rings of “specialized” tissue, considered as the precursors of the CCS, can be distinguished from the surrounding working myocardium (Jongbloed et al., 2008; Wenink, 1976). During maturation these rings will fuse and form extensions. In normal circumstances certain parts should lose their specialized character or disappear by apoptosis as maturing continues. However, solitary cells, interstructural connections, or entire branches sometimes persist as remnants of the primary CCS (Hucker et al., 2008; Inoue & Becker, 1998; Katritsis & Becker, 2007; Kurosawa & Becker, 1985; McGuire et al., 1994, 1996; Szili-Torok et al., 2012), a finding that might also be the result of inappropriate maturation of the primary CCS in NCCM. Such cells may become the origin of ectopic focal triggered activity (Jongbloed et al., 2008). If extensions are long enough to reach the AMC, the outflow tract, the septum, or other adjacent structures, they can provide a substrate for reentrant or nonreentrant arrhythmias involving these regions.

In addition, epithelial-derived cells (EPDCs) play a crucial role in myocardial compaction (Gittenberger-de Groot et al., 1998), induction of purkinje fiber (PF) and bundle fascicle/branch formation (Franco & Icardo, 2001; Lie-Venema et al., 2007; Moorman et al., 1998; Poelmann et al., 2004), and AV junction insulation (Eralp et al., 2006; Gittenberger-de Groot et al., 1998; Kolditz et al., 2007; Kruzynska-Freitag et al., 2001; Wessels et al., 1996). Inappropriate fascicle and PF development might result in focal triggered automaticity, which could explain the occurrence of PVCs originating from the fascicles, as seen in this study.

TABLE 2 Origin of PVC with associated ECG characteristics

No	Age at PVC	Origin of PVCs	FU	BBB morph	Axis	Transition	I	V1	aVR	Inf notch
1	42	PMF	Yes	RBBB	Right superior	$>V4, \leq V5$	rS	R	Pos	No notch
2	30	USF	Yes	Narrow	Right	None	rS	RS	Neg	Notch R
3	40	(RV) septum	No	LBBB	Right	$>V4, \leq V5$	rs	rS	Neg	Notch R
	39	PMF	Yes	RBBB	Left superior	None	Rs	qrs	Neg	Notch Q
4	56	RVOT	No	LBBB	Inferior	$>V3, \leq V4$	qrs	rS	Neg	Notch R
	55	PMF	Yes	RBBB	Right superior	$>V4, \leq V5$	rS	RR'	Pos	Notch Q
5	23	RVOT	No	LBBB	Inferior	$>V4, \leq V5$	qs	rS	Neg	Notch R
6	43	LVOT	Yes	Narrow	Normal	None	Rs	QR	Neg	Notch R
7	54	RVOT/LVOT	No	LBBB	Left superior	$>V2, \leq V3$	R	rS	Neg	Notch R
8	39	LVOT	No	LBBB	Left superior	None	rS	R	Neg	Notch R
9	66	LVOT	No	LBBB	Left superior	None	rS	Rs	Neg	Notch R
10	24	PMF	Yes	RBBB	Right superior	$>V4, \leq V5$	rS	qRR'	Pos	Notch Q
11	76	RVOT	No	LBBB	Normal	$>V3, \leq V4$	QS	rS	Neg	Notch R
12	25	PMF	Yes	RBBB	Left superior	$>V3, \leq V4$	qR	R	Pos	No notch
13	80	PMF	Yes	RBBB	Left superior	None	qR	R	Pos	Notch R
14	52	FW RV	No	LBBB	Normal	$>V4, \leq V5$	qrs	QS	Neg	Notch R
15	24	Septal TA	No	LBBB	Left superior	$>V3, \leq V4$	R	QS	Neg	Notch Q
	24	RVOT	No	LBBB	Normal	$>V3, \leq V4$	Rq	QS	Neg	No notch
	24	FW TA	No	LBBB	Left superior	$>V4, \leq V5$	R	rS	Neg	Notch Q
16	32	SL MA	No	RBBB	Right	None	QS	R	Neg	Notch R

BBB, bundle branch block; FW, free wall; FU, fast upstroke; inf, inferior; LV, left ventricle; LVOT, left ventricular outflow tract; MA, mitral annulus; morf, morphology; PMF, posteromedial fascicle; PVC, premature ventricular contraction; RV, right ventricle; RVOT, right ventricular outflow tract; SL, superolateral; TA, tricuspid annulus; USF, upper septal fascicle. Superior rightward axis: between -90° and -180° , rightward axis: between 90° and 180° , normal axis: between 0° and 90° , and leftward axis: between 0° and -90° .

TABLE 3 Origin of PVCs with associated ECG characteristics, and segmental location of noncompaction

No	Age at PVC	Previous VT	Origin of PVCs	LV segments affected with NC	PVCs originating from a NC LV segment
1	42	Yes	PMF	10, 11, 13–17	No
2	30	No	USF	7, 10, 13–17	No
3	40	No	RV septum	6, 7, 9–11, 13–17	Yes
	39		PMF		No
4	56	Yes	RVOT	2, 7–10, 13–17	No
	55		PMF		No
5	23	Yes	RVOT	4, 8–11, 14–17	No
6	43	Yes	LVOT	2, 4, 7–10, 14–17	No
7	54	No	RVOT/LVOT	2, 3, 4, 7–11, 13–17	No
8	39	Yes	LVOT	7, 8, 10, 11, 13–17	No
9	66	No	LVOT	2–4, 8–10, 14–17	No
10	24	No	PMF	7, 9, 10, 14–17	No
11	76	No	RVOT	9, 10, 14, 15, 16, 17	No
12	25	Yes	PMF	7–10, 14, 15, 17	No
13	80	Yes	PMF	2, 7–11, 13–17	No
14	52	Yes	FW RV	10, 11, 13–17	No
15	24	Yes	Septal TA	2, 5, 7–11, 13–17	No
	24		Septal RVOT		No
	24		FW TA		No
16	32	Yes	SL MA	8, 10, 11, 13–17	No

BBB, bundle branch morphology; FW, free wall; LV, left ventricle; LVOT, left ventricular outflow tract; MA, mitral annulus; NC, noncompaction; PMF, posteromedial fascicle; PVC, premature ventricular contraction; RV, right ventricle; RVOT, right ventricular outflow tract; SL, superolateral; TA, tricuspid annulus; USF, upper septal fascicle; VT, ventricular tachycardia.

FIGURE 4 Apical echocardiographic views in a NCCM patient with PVCs originating from the RVOT. This example shows the lack of correlation between the PVC origin and desegmental location of NC. (A) 12-lead ECG of the RVOT PVC. (B–D) Transthoracic echocardiography showing an apical three- (B), two- (C), and four- (D) chamber view. NCCM, noncompaction cardiomyopathy; PVC, premature ventricular contraction; RVOT, right ventricular outflow tract; TA, tricuspid annulus

3.2 | Possible clinical impact

Identification of the mechanism of the arrhythmogenesis is of paramount interest to tailor the therapy for this specific patient group. For both prescribing antiarrhythmic drugs and EP testing or ablative therapy, the importance of the underlying pathophysiologic mechanism is of obvious importance. Clinical data now start to point out to an origin of ventricular arrhythmia that is not primarily bound to the noncompacted tissue. Further studies are needed to define the regions where PVCs originate from as the VT regions and to further elucidate the relation to the noncompacted tissue.

3.3 | Limitations of the study

In this study, only a limited number of ECGs with PVCs was recorded in all 12 leads and no 12-lead holter tracings or data from electrophysiological studies were available from our 16 NCCM patients.

To overcome the limitations of this study, an invasive EP study should be conducted in this patient population. To confirm our hypothesis and findings, and for risk stratification, a large prospective study with repetitive 12-lead holter tracings and invasive EP testing should be performed. In addition, it would also be of great interest to target specific NCCM genes involved in impulse generation and propagation.

4 | CONCLUSION

Our data suggest that PVCs in NCCM originate mainly from areas that are not affected echocardiographically by noncompaction.

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CONFLICTS OF INTEREST

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REFERENCES

- Cerqueira, M. D., Weissman, N. J., Dilsizian, V., Jacobs, A. K., Kaul, S., Laskey, W. K., ... Verani, M. S. (2002). American Heart Association Writing Group on Myocardial S, Registration for Cardiac I. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*, 105, 539–542.
- Chen, H., Zhang, W., Li, D., Cordes, T. M., Mark Payne, R., & Shou, W. (2009). Analysis of ventricular hypertrabeculation and noncompaction using genetically engineered mouse models. *Pediatric Cardiology*, 30, 626–634.
- Engberding, R., & Bender, F. (1984). Identification of a rare congenital anomaly of the myocardium by two-dimensional echocardiography: persistence of isolated myocardial sinusoids. *The American Journal of Cardiology*, 53, 1733–1734.
- Eralp, I., Lie-Venema, H., Bax, N. A., Wijffels, M. C., Van Der Laarse, A., Deruiter, M. C., ... Gittenberger-De Groot, A. C. (2006). Epicardium-derived cells are important for correct development of the Purkinje fibers in the avian heart. *The Anatomical Record Part A: Discoveries in Molecular, Cellular, and Evolutionary Biology*, 288, 1272–1280.
- Franco, D., & Icardo, J. M. (2001). Molecular characterization of the ventricular conduction system in the developing mouse heart: Topographical correlation in normal and congenitally malformed hearts. *Cardiovascular Research*, 49, 417–429.
- Gittenberger-de Groot, A. C., Vrancken Peeters, M. P., Mentink, M. M., Gourdie, R. G., & Poelmann, R. E. (1998). Epicardium-derived cells contribute a novel population to the myocardial wall and the atrioventricular cushions. *Circulation Research*, 82, 1043–1052.

- Gourdie, R. G., Harris, B. S., Bond, J., Justus, C., Hewett, K. W., O'Brien, ... Sedmera, D. (2003). Development of the cardiac pacemaking and conduction system. *Birth Defects Research Part C: Embryo Today: Reviews*, 69, 46–57.
- Henderson, D. J., & Anderson, R. H. (2009). The development and structure of the ventricles in the human heart. *Pediatric Cardiology*, 30, 588–596.
- Hucker, W. J., McCain, M. L., Laughner, J. I., Iuzzo, P. A., & Efimov, I. R. (2008). Connexin 43 expression delineates two discrete pathways in the human atrioventricular junction. *Anatomical Record*, 291, 204–215.
- Chida, F., Hamamichi, Y., Miyawaki, T., Ono, Y., Kamiya, T., Akagi, T., ... Tomimatsu, H. (1999). Clinical features of isolated noncompaction of the ventricular myocardium: Long-term clinical course, hemodynamic properties, and genetic background. *Journal of the American College of Cardiology*, 34, 233–240.
- Inoue, S., & Becker, A. E. (1998). Posterior extensions of the human compact atrioventricular node: A neglected anatomic feature of potential clinical significance. *Circulation*, 97, 188–193.
- Jenni, R., Oechslin, E., Schneider, J., Attenhofer Jost, C., & Kaufmann, P. A. (2001). Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: A step towards classification as a distinct cardiomyopathy. *Heart*, 86, 666–671.
- Jongbloed, M. R., Mahtab, E. A., Blom, N. A., Schalij, M. J., & Gittenberger-de Groot, A. C. (2008). Development of the cardiac conduction system and the possible relation to predilection sites of arrhythmogenesis. *The Scientific World Journal*, 8, 239–269.
- Josephson, M. E. (2008). *Clinical cardiac electrophysiology. Techniques and interpretations*, 4th edn. (pp. 446–643). Philadelphia: Lippincott Williams & Wilkins.
- Katritsis, D. G., & Becker, A. (2007). The atrioventricular nodal reentrant tachycardia circuit: A proposal. *Heart Rhythm*, 4, 1354–1360.
- Kobza, R., Jenni, R., Erne, P., Oechslin, E., & Duru, F. (2008). Implantable cardioverter-defibrillators in patients with left ventricular noncompaction. *Pacing and Clinical Electrophysiology*, 31, 461–467.
- Kolditz, D. P., Wijffels, M. C., Blom, N. A., van der Laarse, A., Markwald, R. R., Schalij, M. J., & Gittenberger-de Groot, A. C. (2007). Persistence of functional atrioventricular accessory pathways in postseptated embryonic avian hearts: Implications for morphogenesis and functional maturation of the cardiac conduction system. *Circulation*, 115, 17–26.
- Kruzynska-Freitag, A., Machnicki, M., Rogers, R., Markwald, R. R., & Conway, S. J. (2001). Periostin (an osteoblast-specific factor) is expressed within the embryonic mouse heart during valve formation. *Mechanisms of Development*, 103, 183–188.
- Kurosawa, H., & Becker, A. E. (1985). Dead-end tract of the conduction axis. *International Journal of Cardiology*, 7, 13–20.
- Lie-Venema, H., van den Akker, N. M., Bax, N. A., Winter, E. M., Maas, S., Kekarainen, T., ... Gittenberger-de Groot, A. C. (2007). Origin, fate, and function of epicardium-derived cells (EPDCs) in normal and abnormal cardiac development. *The Scientific World Journal*, 7, 1777–1798.
- McGuire, M. A., de Bakker, J. M., Vermeulen, J. T., Opthof, T., Becker, A. E., & Janse, M. J. (1994). Origin and significance of double potentials near the atrioventricular node. Correlation of extracellular potentials, intracellular potentials, and histology. *Circulation*, 89, 2351–2360.
- McGuire, M. A., de Bakker, J. M., Vermeulen, J. T., Moorman, A. F., Loh, P., Thibault, B., ... Janse, M. J. (1996). Atrioventricular junctional tissue. Discrepancy between histological and electrophysiological characteristics. *Circulation*, 94, 571–577.
- Moorman, A. F., de Jong, F., Denyn, M. M., & Lamers, W. H. (1998). Development of the conduction system. *Circulation Research*, 82, 629–644.
- Poelmann, R. E., Jongbloed, M. R., Molin, D. G., Fekkes, M. L., Wang, Z., Fishman, G. I., ... Gittenberger-de Groot, A. C. (2004). The neural crest is contiguous with the cardiac conduction system in the mouse embryo: A role in induction? *Anatomy and Embryology*, 208, 389–393.
- Ritter, M., Oechslin, E., Sutsch, G., Attenhofer, C., Schneider, J., & Jenni, R. (1997). Isolated noncompaction of the myocardium in adults. *Mayo Clinic Proceedings*, 72, 26–31.
- Szili-Torok, T., van Malderen, S., & de Groot, N. (2012). Born with a 'dead'-end-tract resulting in arrhythmias in the aorto-mitral continuity: Coincidence, causation, and 'commensuration'. *Europace*, 14, 308–309.
- Wenink, A. C. (1976). Development of the human cardiac conducting system. *Journal of Anatomy*, 121, 617–631.
- Wessels, A., Markman, M. W., Vermeulen, J. L., Anderson, R. H., Moorman, A. F., & Lamers, W. H. (1996). The development of the atrioventricular junction in the human heart. *Circulation Research*, 78, 110–117.

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