

MDPI

Communication

# Variability in Anesthesia Models of Care in Cardiac Surgery

Dianne McCallister <sup>1</sup>, Bethany Malone <sup>2</sup>, Jennifer Hanna <sup>3</sup> and Michael S. Firstenberg <sup>4</sup>,\*

- Diagnosis Well, Inc., Greenwood Village, CO 80111, USA; diannemcca12@gmail.com
- Department of Surgery, Summa Akron City Hospital, Akron, OH 44304, USA; Bcbmalone@gmail.com
- Department of Cardiothoracic and Vascular Surgery, The Medical Center of Aurora, Aurora, CO 80012, USA; hannaj21@hotmail.com
- William Novick Global Cardiac Alliance, Memphis, TN 38104, USA
- \* Correspondence: msfirst@gmail.com

**Abstract:** The operating room in a cardiothoracic surgical case is a complex environment, with multiple handoffs often required by staffing changes, and can be variable from program to program. This study was done to characterize what types of practitioners provide anesthesia during cardiac operations to determine the variability in this aspect of care. A survey was sent out via a list serve of members of the cardiac surgical team. Responses from 40 programs from a variety of countries showed variability across every dimension requested of the cardiac anesthesia team. Given that anesthesia is proven to have an influence on the outcome of cardiac procedures, this study indicates the opportunity to further study how this variability influences outcomes and to identify best practices.

**Keywords:** cardiothoracic surgery; anesthesia staffing models; outcomes; operating room staffing; handoffs; quality; communication



Citation: McCallister, D.; Malone, B.; Hanna, J.; Firstenberg, M.S. Variability in Anesthesia Models of Care in Cardiac Surgery. *Surgeries* 2021, 2, 1–8. https://doi.org/ 10.3390/surgeries2010001

Received: 24 November 2020 Accepted: 31 December 2020 Published: 6 January 2021

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

#### 1. Introduction

The operating room is a complex environment, with multiple team members, many of whom may move on and off the team based on shifts and other factors. There is growing evidence that how various members of the operating room team interact and function with regard to their models of care impact, in either a positive or negative way, patient mortality rates, readmissions, and major complications [1]. However, few studies address the diversity which includes how many and what training is actually being provided for anesthesia and other necessary intra-operative services, nor the impact that such diversity has on clinical outcomes [2–4]. The aim of this study is to characterize what types of practitioners provide anesthesia services during cardiac operations. We hypothesize that there exists a large variability in the composition, structure, and functioning of the anesthesia-providing team in cardiac surgery across programs.

## 2. Materials and Methods

An anonymous online survey was sent out to international cardiac surgery programs. No statistical analysis was performed due to the low number of responses and the large variability in responses. This finding helps support the hypothesis that there exists a large variability in how (and by whom) cardiac surgical patients are managed in the operating room.

The survey was distributed via a closed-membership international "listserv" internet-based communication forum (OpenHeart-L@lists.hsforum.com), an international community of cardiothoracic surgeons, related providers (i.e., cardiac anesthesiologist, nursing, etc.), representatives of industry, and interested members of the lay community. As of December 2020, the forum consisted of 524 individual members. However, due to the nature of the forum, no active demographics are tracked and hence it is unknown how many separate programs or non-surgeons are represented. Only active practicing cardiac surgeons

were asked to participate (this was confirmed via self-reporting after completion of the survey). There is no charge for membership. The system is administered and moderated by the Heart Surgery Forum Journal and supported by the publisher—Carden Jennings Publishing Co., Ltd. Charlottesville, VA USA) (https://journal.hsforum.com/index.php/HSF). The survey (Appendix A) was distributed as a hyperlink within an email inviting forum members to participate. No incentives for completion were provided. The survey was open, starting in 2015, for responses for 4 months with reminders sent each month to the entire forum. Voluntary responses were obtained from 40 programs.

#### 3. Results

The distribution in program sizes and responses is illustrated in Table 1. For smaller programs (<200 cases/year), 38% have certified registered nurse anesthetists (CRNA) managing cardiac patients with 62% having only physician anesthesiologists involved in the intra-operative management. Likewise, for medium programs (201–749 cases per year), 35% have CRNAs (65% physicians only) and for larger programs (>750 cases per year), one-third use CRNAs (two-thirds, physicians only).

TT 11 4	C 1:			1.	/
Table 1.	Cardiac surgery pro	ogram size (	maior ca	irdiac cases.	/vear).
	Caracac Sanger, pre	5-4		ir direct coloco,	,

Major Cases (Per Year)	Respondents $(n = 40)$			
Small Programs				
51–100	2 (5%)			
101–150	3 (7.5%)			
151–200	10 (25%)			
Medium l	Programs			
201–250	3 (7.5%)			
251–300	2 (5%)			
301–400	1 (2.5%)			
401–500	5 (12.5%)			
501–750	1 (2.5%)			
Large Pr	ograms			
>750	13 (32.5%)			

For smaller programs, only 1 of 15 (6.7%) programs that responded have a formal cardiothoracic residency or fellowship training program. However, 50% of medium sized programs (201–749 cases, n = 12) reported having a training program while 77% (n = 10/13) of larger programs have training programs with residents or fellows involved in cardiac surgery cases. Table 2 illustrates the spectrum of who is involved in the management of patients and characteristics that help describe the nature and complexity of the specific programs (i.e., whether a program performs ventricular assist devices, transplants, catheter-based structural heart interventions). Table 2 also outlines whether various types of trainees are involved in the intra-operative care of cardiac surgery patients, employment status of anesthesia providers, and country of origin. Table 3 lists the breakdown of number of programs and their size by country.

Table 2. Intra-operative management.

Dedicated Cardiothoracic Anesthesiologist (MD/DO) †	28 (70%)			
Use of CRNAs				
Yes	15 (37.5%)			
No—MD/DO attendings only	16 (40%)			
No—MD/DO attendings with anesthesia residents	9 (22.5%)			

 Table 2. Cont.

Dedicated Cardiothoracic Anesthesiologist (MD/DO) †	28 (70%)
Intraoperative TEE	
All cardiac cases	30 (75%)
Only valves and intra-cardiac cases	7 (17.5%)
Only valves, intra-cardiac cases, also high-risk CABG only *	3 (7.5%)
Who performs TEE	·
>50% of time, anesthesia team	5 (12.5%)
>80% of time, anesthesia team	6 (15%)
All performed by anesthesia	23 (57.5%)
All performed by cardiologist	5 (12.5%)
Training Program	0 (12.070)
CRNA	7 (17 59/ )
	7 (17.5%)
General Surgery Residency	11 (27.5%)
Cardiothoracic Surgery Fellowship	9 (22.5%)
Anesthesia Residency	3 (7.5%)
Cardiothoracic Anesthesia Fellowship	5 (12.5%)
Cardiology Fellowship	2 (5%)
Medical students only	1 (2.5%)
Multiple training programs **	12 (30%)
No training programs	17 (42.5%)
LVAD/Transplant Program	17 (12.0 /0)
No	21 (52.5%)
	· · · · · · · · · · · · · · · · · · ·
No, but developing	2 (5%)
Bridge only	3 (7.5%)
DT only	2 (5%)
DT/Bridge	4 (10%)
LVAD and Transplant	5 (12.5%)
Percutaneous Valve (TAVR) Program	
No	20 (50%)
Developing	4 (10%)
>20 implants/yr	7 (17.5%)
>50 implants/yr	9 (22.5%)
Anesthesia Hospital Employed	
No	15 (37.5%)
CRNA only employed	4 (10%)
Physician only employed	5 (12.5%)
CRNA and MD	15 (37.5%)
Country of Response	, ,
USA	25 (62.5%)
India	3 (7.5%)
Australia	· · · · · ·
	2 (5%)
Columbia	1 (2.5%)
Croatia	1 (2.5%)
Argentina	1 (2.5%)
Equadro	1 (2.5%)
<sup>1</sup> UK	1 (2.5%)
Italy	1 (2.5%)
Israel	1 (2.5%)
Canada	1 (2.5%)
Russia	1 (2.5%)
Saudi Arabia	1 (2.5%)

Adult cases: estimated number of major cardiac surgical procedures performed annually requiring cardiopulmonary bypass or off-pump techniques (i.e., off-pump coronary artery bypass); CABG: coronary artery bypass grafting surgery; MD/DO: medical or osteopathic physicians; TEE: transesophageal echocardiography; CRNA:

Certified Registered Nurse anesthetists; LVAD/Transplant Program: Program performs implantation of left ventricular assist devices (LVAD) and/or cardiothoracic transplantation; DT: destination therapy LVAD implantation; Bridge: LVAD bridge to transplant; TAVI: Trans-aortic valve implantation. † Dedicated cardiothoracic anesthesiologist was defined as an anesthesiologist with advanced, fellowship and/or specialty training in cardiothoracic surgery. \* High-risk CABG cases as defined by local team providers on a case-by-case basis. \*\* Multiple training programs was defined as having more than 1 type of trainee potentially involved in cardiac patient care (i.e., thoracic residents and anesthesia residents).

Table 3. Program size by country.

Country	Program Size (Number of Programs)	
	51–100 cases ( <i>n</i> = 2)	
	101-150 cases $(n=3)$	
	151-200  cases  (n=5)	
	201-250 cases $(n=3)$	
USA	251-300 cases $(n=2)$	
	301-400 cases $(n=2)$	
	401-500 cases $(n=2)$	
	501-750 cases $(n=1)$	
	>750 cases $(n = 5)$	
	151-200 cases $(n=1)$	
India	401-500 cases $(n=1)$	
	>750 cases $(n = 1)$	
A 1:	401-500 cases $(n=1)$	
Australia Columbia Croatia	>750 cases $(n = 1)$	
	301-400 cases $(n=1)$	
	401-500 cases $(n = 1)$	
Argentina	401-500 cases $(n=1)$	
Equador	51-100  cases  (n=1)	
United Kingdom	>750 cases $(n = 1)$	
Italy	>750 cases $(n = 1)$	
Israel	>750 cases $(n = 1)$	
Canada	>750 cases $(n = 1)$	
Russia	>750 cases $(n = 1)$	

## 4. Discussion

The analysis of the data supplied from the programs show variability across every dimension, even when grouped by similar size, and by teaching/non-teaching programs of the same size. This is despite the fact that all United States programs are held to the same standard in terms of their outcomes by Society of Thoracic Surgery (STS) reporting standards. Furthermore, there is growing expectation that such outcomes be publicly reported, and such data is potentially used for hospital reimbursements or by patients to decide who and where to have their cardiovascular care.

The results of this survey carry important implications. There are multiple studies that suggest that case volumes of programs impact outcomes, particularly in valve surgeries [5,6]. This is leading to discussions and reimbursement hurdles that in the future may prevent certain small volume programs from accessing advanced technologies such as catheter-based or hybrid structural procedures. In addition, the increasing case complexity in cardiac surgery involves longer, more tedious cases, in which handoffs can prevent morbidity produced as a side-effect of provider fatigue, but such models require additional providers to cover these breaks and transitions [7]. While the primary attending surgeon rarely changes during the procedure, it is not uncommon for members of other operative teams to change, which is driven by resident duty hour restrictions [8] and the duty hours of other staff and team members. Evidence clearly exists that anesthesia handoffs intraoperatively adversely affect both morbidity and mortality in cardiac surgery patients [9]. However, the frequency of such events, the provider make-ups of the team, and specific

models of care remain poorly defined. As demonstrated by our brief survey, there is large variability in the composition and functioning of the anesthesia-providing team. While the STS has incorporated an anesthesia-specific component of their data collection system, few questions deal specifically with the care model structure and function [10].

In order to reduce operative mistakes, preoperative checklists and team briefings have been shown to reduce communication errors, especially with multidisciplinary teams that include nurses, surgeons, anesthesiologists, and residents [11]. A similar system has yet to be developed for intra-operative handoffs.

Our data opens the question of team experience, the use of anesthesia providers, and the type of anesthesia providers used in cardiac surgery/procedures and raises the question regarding what potential relationship this has to outcomes. Previous work in this area has tried to study the relationships between anesthesiologist productivity as related to the impact on solo attending cases versus those performed in conjunction with residents or CNRA's [12]. While Posner's findings suggested that in a large university program outcomes were not impacted by team composition, productivity, or concurrency, she acknowledged that the role of specific individuals was not studied. More recent work has supported these findings by reviewing a national claims database of 443,000 Medicare beneficiaries [13]. In this study, there were no significant differences observed between different care models and costs, length of stay, and/or mortality. Conversely, Liu and colleagues raised concern that anesthesia-specific outcomes were much worse in Taiwan when compared to other developed countries (United States, United Kingdom, and Japan) and speculated that various aspects of care models and provider training quality might play a role [14]. Of note, none of these studies explored cardiac surgery procedure specifically and hence it is difficult to extrapolate their general results to the specific challenges that cardiac surgery procedures often entail (i.e., invasive monitoring, use of cardiopulmonary bypass, active temperature management, hemodynamic instability, trans-esophageal echocardiography, complex/poorly controlled comorbidities, etc.). Studies specifically exploring the role of anesthesia and various models of care in cardiac surgical cases suggest that patient factors have the greatest impact on outcomes, followed by surgeon variables. However, these studies do acknowledge the potential role that anesthesia related variables—such as team composition, models of care, volume of cases, and overall experience—might have on outcomes [2–4]. Hence, as suggested by our findings and advocated by others including the Society of Thoracic Surgeons (STS), Society of Cardiovascular Anesthesiologists (SCA), and the Association of Cardiothoracic Anaesthetists (ACTA), there is a need to better understand the influences on non-surgeon providers during cardiac surgical procedures and outcomes [10,15].

While the hypothesis of this study is the assumption that variabilities in anesthesia care models exist, the extension of this concept is that such variabilities potentially have an impact on patient outcomes. While there is a natural assumption that the surgeon has the largest impact on patient outcome, particularly in the context of the technical aspects of the procedure (quality of anastomosis, myocardial protection, tissue trauma, response to unusual and/or unexpected intra-operative findings, etc.) there is literature to suggest that the role of a surgeon, regardless of experience, is only one variable impacting patient outcomes [16]. In fact, there is growing evidence to suggest that the operating surgeon has little role in preventing most adverse outcomes after cardiac surgery [17]. As such, it is imperative to better understand those other factors that impact outcomes; hence, our hypothesis that variabilities exist in anesthesia care delivery models. Our findings as discussed above, will hopefully lay the foundation for exploring relationships between different models of care—and potentially even different providers or types of providersand their impact on patient post-operative outcomes. Again, while the technical expertise and judgment of the surgeon has an obvious role in outcomes, it is a reasonable assumption that similar experiences, cognitive and technical interventions, training, and responses to intra-operative events by members of the anesthesia team also have an impact. Defining the magnitude of that impact and opportunities for improvement should be explored.

As mentioned above, these concepts serve as the foundation for the development of a joint database between the Society of Cardiovascular Anesthesiologists and the Society of Thoracic Surgeons [10].

Given the programmatic implications to programs and clinical practice, our study suggests that the exploration of these factors deserve more study in the quest to improve patient outcomes and provide guidance to the teams most effective in achieving this goal.

#### 5. Limitations

The major limitation of this study is the small number of reported cases, specifically the low number of responses from programs outside of the United States. While the limited number of responses combined with the inherent variabilities as reported makes it difficult to draw clearly defined conclusions, our findings do support the hypothesis that there are large variabilities in how anesthesia care is delivered to patients undergoing cardiac surgery. Furthermore, the overall response rate (<10% of forum members responded) is low, such response rates and methodological issues are not uncommon with medical, internet-based, voluntary surveys [18,19].

#### 6. Conclusions

Our study shows that there is variability, across every dimension of the international CT programs in regard to anesthesia in the role and staffing of anesthesia providers. Given the potential role of the anesthesia team on patient outcomes, this study suggests the opportunity for further investigation. Hopefully, further research can investigate the influence of different models on patient outcomes to help define best practices.

**Author Contributions:** All authors contributed to the initial hypothesis, methods design, data analysis, and writing and reviewing of the manuscript. All authors have contributed substantially to the work reported. All authors have read and agreed to the published version of the manuscript.

Funding: No additional or external funding supported this work.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author

Conflicts of Interest: The authors declare no conflict of interest.

## Appendix A Cardiothoracic Anesthesia Models of Care Survey

## 1. Adult Cases Annually—Pick One

51-100

101-150

151-200

201-250

251-300

301-400

#### 2. Dedicated Cardiothoracic Anesthesia/CRNA's—Pick One

No—attendings only

No-attendings and residents

Used in cardiothoracic cases

Used in thoracic cases only

## 3. Intraoperative TEE—Pick One

All cardiac cases

All valves and intra-cardiac cases

All valves, intra-cardiac cases, but high-risk CABG only

## 4. Who performs TEE—Pick One

>50% anesthesia team >80% anesthesia team All performed by anesthesia All performed by cardiologist

## 5. Training Program—Select as Many as Applicable

**CRNA** 

General Surgery Residency
Cardiothoracic Surgery Fellowship
Anesthesia Residency
Cardiothoracic Anesthesia Fellowship
Cardiology Fellowship
Medical students only
Multiple training programs
No training programs

## 6. LVAD/Transplant Program—Pick One

No
No, but developing
Bridge to transplant only
Destination therapy only
Destination therapy and bridge
LVAD and transplant

## 7. TAVI program—Pick One

No Developing a program >20 implants/yr >50 implants/yr

### 8. Anesthesia Hospital Employed—Pick One

No CRNA only Physician only CRNA and MD

## 9. Country of Program—Enter Text

## References

- 1. Jones, P.M.; Cherry, R.A.; Allen, B.N.; Jenkyn, K.M.B.; Shariff, S.Z.; Flier, S.; Vogt, K.N.; Wijeysundera, D.N. Association Between Handover of Anesthesia Care and Adverse Postoperative Outcomes Among Patients Undergoing Major Surgery. *JAMA* 2018, 319, 143–153. [CrossRef] [PubMed]
- 2. Papachristofi, O.; Mackay, J.H.; Powell, S.J.; Nashef, S.A.; Sharples, L. Impact of the Anesthesiologist and Surgeon on Cardiac Surgical Outcomes. *J. Cardiothorac. Vasc. Anesth.* **2014**, *28*, 103–109. [CrossRef] [PubMed]
- 3. Gani, F.; Kim, Y.; Weiss, M.J.; Makary, M.A.; Wolfgang, C.L.; Hirose, K.; Cameron, J.L.; Wasey, J.O.; Frank, S.M.; Pawlik, T.M. Effect of surgeon and anesthesiologist volume on surgical outcomes. *J. Surg. Res.* **2016**, 200, 427–434. [CrossRef] [PubMed]
- 4. Glance, L.G.; Hannan, E.L.; Fleisher, L.A.; Eaton, M.P.; Dutton, R.P.; Lustik, S.J.; Li, Y.; Dick, A.W. Feasibility of Report Cards for Measuring Anesthesiologist Quality for Cardiac Surgery. *Anesth. Analg.* **2016**, *122*, 1603–1613. [CrossRef] [PubMed]
- 5. Badhwar, V.; Vemulapalli, S.; Mack, M.A.; Gillinov, A.M.; Chikwe, J.; Dearani, J.A.; Grau-Sepulveda, M.V.; Habib, R.; Rankin, J.S.; Jacobs, J.P.; et al. Volume-Outcome Association of Mitral Valve Surgery in the United States. *JAMA Cardiol.* **2020**, *5*, 1092–1101. [CrossRef] [PubMed]
- 6. Chikwe, J.; Toyoda, N.; Anyanwu, A.C.; Itagaki, S.; Egorova, N.N.; Boateng, P.; El-Eshmawi, A.; Adams, D.H. Relation of Mitral Valve Surgery Volume to Repair Rate, Durability, and Survival. *J. Am. Coll. Cardiol.* **2017**, *69*, 2397–2406. [CrossRef] [PubMed]
- 7. Warltier, D.C.; Howard, S.K.; Rosekind, M.R.; Katz, J.D.; Berry, A.J. Fatigue in Anesthesia: Implications and Strategies for Patient and Provider Safety. *Anesthesiol. J. Am. Soc. Anesthesiol.* **2002**, *97*, 1281–1294. [CrossRef] [PubMed]

8. Ahmed, N.; Devitt, K.S.; Keshet, I.; Spicer, J.; Imrie, K.; Feldman, L.; Cools-Lartigue, J.; Kayssi, A.; Lipsman, N.; Elmi, M.; et al. A systematic review of the effects of resident duty hour restrictions in surgery: Impact on resident wellness, training, and patient outcomes. *Ann. Surg.* **2014**, 259, 1041–1053. [CrossRef] [PubMed]

- 9. Hudson, C.C.; McDonald, B.; Hudson, J.K.; Tran, D.; Boodhwani, M. Impact of anesthesia handover on mortality and morbidity in cardiac surgery: A cohort study. *J. Cardiothorac. Vasc. Anesth.* **2015**, 29, 11–16. [CrossRef] [PubMed]
- 10. Del Rio, J.M.; Abernathy, J.J., III; Taylor, M.A.; Habib, R.H.; Fernandez, F.G.; Bollen, B.A.; Lauer, R.E.; Nussmeier, N.A.; Glance, L.G.; Petty, J.V., III; et al. The Adult Cardiac Anesthesiology Section of STS Adult Cardiac Surgery Database: 2020 Update on Quality and Outcomes. *Anesth. Analg.* 2020, 131, 1383–1396. [CrossRef] [PubMed]
- 11. Lingard, L.; Regehr, G.; Orser, B.; Reznick, R.; Baker, G.R.; Doran, D.; Espin, S.; Bohnen, J.; Whyte, S. Evaluation of a Preoperative Checklist and Team Briefing Among Surgeons, Nurses, and Anesthesiologists to Reduce Failures in Communication. *Arch. Surg.* 2008, 143, 12–17. [CrossRef] [PubMed]
- 12. Posner, K.L.; Freund, P.R. Trends in Quality of Anesthesia Care Associated with Changing Staffing Patterns, Productivity, and Concurrency of Case Supervision in a Teaching Hospital. *J. Am. Soc. Anesthesiol.* **1999**, *91*, 839–847. [CrossRef] [PubMed]
- 13. Sun, E.C.; Miller, T.R.; Moshfegh, J.; Baker, L.C. Anesthesia Care Team Composition and Surgical Outcomes. *Anesthesiology* **2018**, 129, 700–709. [CrossRef] [PubMed]
- Liu, T.-C.; Wang, J.-O.; Chau, S.-W.; Tsai, S.-K.; Wang, J.-J.; Chen, T.-L.; Tsai, Y.-C.; Ho, S.-T. Survey of 11-year Anesthesia-related Mortality and Analysis of its Associated Factors in Taiwan. Acta Anaesthesiol. Taiwanica 2010, 48, 56–61. [CrossRef]
- 15. Papachristofi, O.; Sharples, L.D.; Mackay, J.H.; Nashef, S.A.M.; Fletcher, S.N.; Klein, A.A.; Association of Cardiothoracic Anaesthetists (ACTA); Lau, G.; Woodward, D.; Hillier, J.; et al. The contribution of the anaesthetist to risk-adjusted mortality after cardiac surgery. *Anaesthesia* 2015, 71, 138–146. [CrossRef] [PubMed]
- 16. Edwards, F.H.; Ferraris, V.A.; Kurlansky, P.A.; Lobdell, K.W.; He, X.; O'Brien, S.M.; Furnary, A.P.; Rankin, J.S.; Vassileva, C.M.; Fazzalari, F.L.; et al. Failure to Rescue Rates after Coronary Artery Bypass Grafting: An Analysis from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *Ann. Thorac. Surg.* 2016, 102, 458–464. [CrossRef] [PubMed]
- 17. Westaby, S.; De Silva, R.; Petrou, M.; Bond, S.; Taggart, D.P. Surgeon-specific mortality data disguise wider failings in delivery of safe surgical services. *Eur. J. Cardio-Thorac. Surg.* **2014**, *47*, 341–345. [CrossRef] [PubMed]
- 18. Aitken, C.; Power, R.; Dwyer, R. A very low response rate in an on-line survey of medical practitioners. *Aust. N. Z. J. Public Health* **2008**, 32, 288–289. [CrossRef] [PubMed]
- 19. Blumenberg, C.; Barros, A.J. Response rate differences between web and alternative data collection methods for public health research: A systematic review of the literature. *Int. J. Public Health* **2018**, *63*, 765–773. [CrossRef] [PubMed]