Clinical and Echocardiographic Outcomes after Aortic Valve Repair in Patients with Bicuspid or Unicuspid Aortic Valve

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ABSTRACT: **Background:** Unicuspid and bicuspid aortic valve (BAV) are congenital cardiac anomalies associated with valvular dysfunction and aortopathies occurring at a young age.

Objectives: To evaluate our experience with aortic valve repair (AVr) in patients with bicuspid or unicuspid aortic valves.

Methods: Eighty patients with BAV or unicuspid aortic valve (UAV) underwent AVr. Mean patient age was 42 ± 14 years and 94% were male. Surgical technique included: aortic root replacement with or without cusp repair in 43 patients (53%), replacement of the ascending aorta at the height of the sinotubular junction with or without cusp repair in 15 patients (19%), and isolated cusp repair in 22 patients (28%).

Results: The anatomical structure of the aortic valve was bicuspid in 68 (85%) and unicuspid in 12 patients (15%). Survival rate was 100% at 5 years of follow-up. Eleven patients (13.7%) underwent reoperation, 8 of whom presented with recurrent symptomatic aortic insufficiency (AI). Late echocardiography in the remaining 69 patients revealed mild AI in 63 patients, moderate recurrent AI in 4, and severe recurrent AI in 2. Relief from recurrent severe AI or reoperations was significantly lower in patients who underwent cusp repair compared with those who did not (P = 0.05). Furthermore, the use of pericardial patch augmentation for the repair was a predictor for recurrence (P = 0.05).

Conclusions: AVr in patients with BAV or UAV is a safe procedure with low morbidity and mortality rates. The use of a pericardial patch augmentation was associated with higher repair failure.

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KEY WORDS: aortic valve sparing surgery, aortic valve repair (AVr), bicuspid aortic valve (BAV), pericardial patch, unicuspid aortic valve (UAV)

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly, with a prevalence of 1–2% in the general population [1,2]. It is associated with valvular complications such as aortic stenosis, mostly in older patients, and aortic insufficiency (AI), occurring more often in younger patients [1]. BAV malformation, independent of valvular function, is also associated with aortopathy and a higher incidence of aortic aneurism and dissection than that found in the general population [2]. The association between BAV and aortopathy can be explained by mechanical factors, such as blood flow through the BAV causing asymmetrical forces to act on the endothelium and genetic factors that increase matrix metalloproteinase and decrease fibrilin-1, a component of the aortic media layer [3].

Unicuspid aortic valve (UAV), unlike BAV, is a rarer congenital valve anomaly that results from the fusion of the three tubercles during embryonic life. UAV shares many of the features of BAV, including valvular dysfunction and aortopathies. These conditions develop at an earlier age and progress at a faster rate in patients with UAV compared to those with BAV [4].

While in the past, root or ascending aorta replacement at the height of the sinotubular junction (STJ) has been used to correct AI in patients with dilatation of the aorta with normal aortic valve leaflets [5] during the last decade these procedures have expanded to include patients with anatomic valve abnormalities, such as BAV and UAV, as well as deformed or calcified tricuspid aortic valve (TAV) [6,7].

Depending on the specific mechanism of regurgitation, there are several procedures that can be performed to repair, rather than replace, a valve in patients with AI. Unicuspid or bicuspid aortic valve repair (AVr) includes root replacement by re-implantation or remodeling techniques, replacement of the ascending aorta at the height of the STJ with an appropriate Dacron graft diameter [8-10], or aortic cusp repair with or without aortic root replacement. AVr should be considered when the estimated repair durability time is at least equal to that of a bioprosthetic valve. AVr in patients with UAV or BAV, who are generally of a young age when referred for surgery, also

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has the advantage of avoiding other complications associated with prosthetic valves and the use of anticoagulation drugs. Furthermore, valve-preserving surgery could be a more favorable procedure for some of these patients, who are at a higher risk for aortopathy.

Some recent studies have reported that the need for cusp repair in patients with BAV who undergo replacement of the ascending aorta or aortic root have higher rates of reoperations or recurrent AI compared to patients with TAV [11,12].

In this study, we examined the early- and later-term results of all patients with either UAV or BAV who underwent AVr in our department between 2004 and 2016.

PATIENTS AND METHODS

Between 2004 and 2016, 227 patients with various degrees of AI underwent either AVr or preservation surgery. Of the total, 80 had a UAV or BAV [Table 1]. We excluded all patients diagnosed with acute or chronic dissection of the aorta. Preoperative, operative, and postoperative data were prospectively collected from our department's database. All clinical and echocardiographic follow-up was carried out via our outpatient clinic. Those lost to ambulatory follow-up were interviewed by telephone. The study was approved by the institutional review board. The mean clinical follow-up (completed by 100% of the patients) was 70 ± 40 months, and the echocardiographic follow-up (completed by 99% of the patients) was 49 ± 41 months. The analysis included a total of 464.3 patient-years of follow-up.

Table 1. Demographic data

	Patients, n=80
Gender, male	75 (93.8)
Age, years	42 ± 14
NYHA functional class, n (%)	
I	48 (60)
II	25 (31.3)
III	7 (8.7)
IV	0 (0)
Diabetes mellitus, n (%)	0 (0)
Hypertension, n (%)	20 (25)
COPD, n (%)	2 (2.5)
Dialysis, n (%)	0 (0)
Ejection fraction	57 ± 7
LVEDD	5.5 ± 0.8
LVESD	3.4 ± 0.8
Aortic root diameter, cm	3.9 ± 0.6
Ascending aorta diameter, cm	4.5 ± 0.8
EuroSCORE I logistic, %	4.2 ± 2.9
Previous cardiac operations, n (%)	6 (7.5)

NYHA = New York Heart Association, COPD = chronic obstructive pulmonary disease, LVEDD = left ventricular end diastolic diameter, LVESD = left ventricular end systolic diameter

SURGICAL PROCEDURE

All patients underwent surgery through a median sternotomy. Standard cardiopulmonary bypass was established by cannulation of the aortic arch for arterial inflow and the right atrium for venous return. Myocardial protection was achieved by using a combination of antegrade and retrograde cold blood cardioplegia.

Surgical techniques included:

- Replacement of the aortic root with or without cusp repair in 43 patients (54%), either by re-implantation using a Gelweave Valsalva graft (Vascutek Ltd, Renfrewshire, Scotland), or by a remodeling procedure using a straight Dacron tube
- Replacement of the ascending aorta at the height of the STJ with or without cusp repair in 15 patients (19%)
- Isolated cusp repair in 22 patients (27%), which included subcommisural annuloplasty [13], circular annuloplasty using a Gore-Tex 0-0 suture (W. L. Gore & Associates, Inc. AZ, USA) [14], partial resection of the aortic cusps due to fibrosis or calcification, cusp plication using a 5-0 polypropylene stitch (Prolene®; Ethicon, Somerville, NJ, USA) in order to reduce the length of the prolapsed aortic cusp [15], and cusp pericardial patch augmentation (autologous glutaraldehyde treated) when there was not enough native cusp tissue after resection [Table 2].

All patients were monitored intraoperatively with transesophageal echocardiography (TEE) for valve repair evaluation.

Postoperative study endpoints included: hospital mortality and morbidity (cerebral vascular accident, transient ischemic attack, acute renal failure, atrial fibrillation, post-pericardiot-

Table 2. Operative data

	Patients, n=80 (%)
Main procedure	
Aortic root replacement	43 (53.7)
With cusp repair	31 (72.1)
Without cusp repair	12 (27.9)
Ascending aorta replacement	15 (18.8)
With cusp repair	11 (73.3)
Without cusp repair	4 (26.7)
Isolated cusp repair	22 (27.5)
Cusp repair maneuver	
Circular annuloplasty	22 (27.5)
Cusp resection	22 (27.5)
Cusp plication	50 (62.5)
Pericardial patch augmentation	16 (20.0)
Subcommisural annuloplasty	10 (12.5)
Concomitant procedures	12 (15.0)
MV repair	8 (10.0)
Tricuspid valve repair	1 (1.25)
MAZE procedure	2 (2.5)
CABG	1 (1.25)
Septal myectomy	1 (1.25)

MV = mitral valve, CABG = coronary artery bypass graft omy syndrome, sternal wound infection, permanent pacemaker implantation), hospital stay, intensive care unit stay, ventilation time, and late outcomes (survival, reoperation on the aortic valve, and recurrent aortic valve regurgitation).

STATISTICAL ANALYSIS

All statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). Values are expressed as mean ± standard deviation for continuous variables, and as frequency and percentage for categorical variables. Reoperation on aortic valve and recurrent aortic valve regurgitation was calculated by the Kaplan–Meier method. Comparison of survival rates between procedure, cusp, and patch was performed using the log-rank test. Multiple Cox regression was carried out to estimate the independent effect of baseline characteristics on recurrent regurgitation and reoperation. P value < 0.05 was considered significant with no correction for multiple testing.

RESULTS

Patient characteristics are shown in Table 1. Mean patient age was 42 ± 14 years, and 93.8% of the patients were male. Good functional state, expressed by New York Heart Association (NYHA) functional class I–II, was 91.3% preoperatively. Echocardiographic findings showed that 42.5% of the patients had AI (≥ 3+), 6.25% had aortic stenosis (≥ 3+), and 10% had mitral regurgitation (≥ 3+). The main indication for surgery was aortic dilatation in 45 patients (56%), AI (≥ 3) with symptoms and/or left ventricular dilatation in 27 patients (34%), severe mitral regurgitation in 7 patients (9%), and endocarditis in one patient (1%). The anatomical structure of the aortic valve was bicuspid in 68 patients (85%) and unicuspid in 12 patients (15%). Six patients had undergone previous surgery: four coarctation of the aorta repair and one closure of the patent ductus arteriosus and balloon dilatation of the pulmonary valve. One patient had a previous AVr.

Cusp repair was performed on 31 of the 43 patients (72.1%) who underwent replacement of the aortic root, and on 11 of the 15 patients (73.3%) who underwent replacement of the ascending aorta at the height of the STJ. Concomitant procedures were performed in 12 patients (15%) [Table 2]. Mean cross-clamp time was 69 ± 32 minutes and mean bypass time was 88 ± 36 minutes.

EARLY OUTCOMES

All patients left the operating room with no more than grade 1 AI according to intraoperative TEE. Mean ventilation time was 11 ± 21 hours, mean intensive care unit stay was 33 ± 36 hours, and mean hospital stay was 5 ± 2 days. There was no in-hospital mortality. One patient, experienced a major postoperative complication with cerebral vascular accident that was expressed with left hemiparesis, which was partially resolved. None of the patients needed re-exploration for bleeding, none required permanent pacemaker implantation, and none had sternal wound infection. There were no cases of perioperative myocardial infarction or renal failure that required dialysis.

LATE OUTCOMES

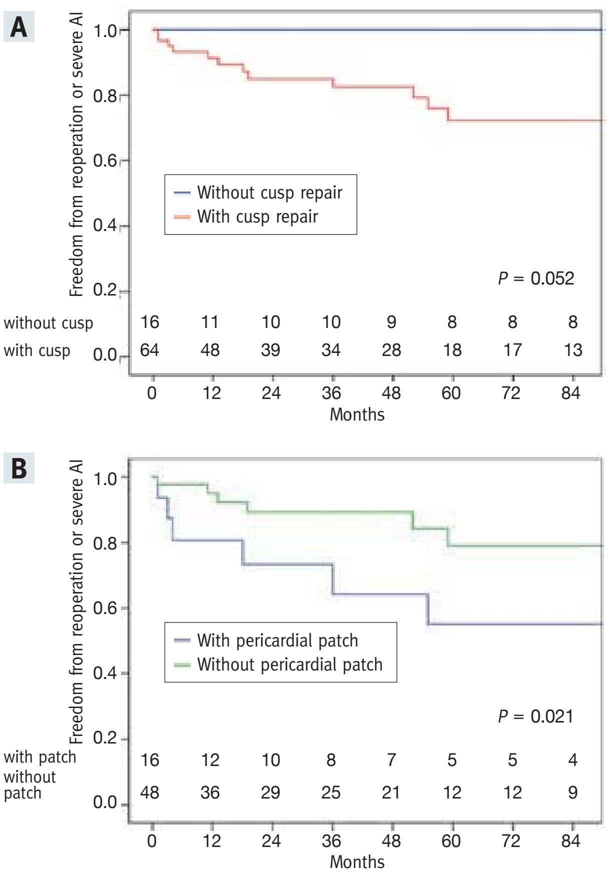
There were no cases of mortality during the 5 years of follow-up, and the overall survival rate was 100%. Seventy-one patients (89%) had NYHA functional class I–II score during follow-up. Eleven patients (13.7%) required reoperation with aortic valve re-intervention; eight due to recurrent symptomatic AI, one due to severe mitral regurgitation with moderate AI, and two because of bacterial endocarditis with an abscess in the aortic root. One of the patients who required reoperation due to recurrent AI was found to have disengagement of the annuloplasty stitch and needed re-repair by annuloplasty. All other patients underwent replacement of the aortic valve: eight received a mechanical prosthetic valve and two a biological prosthetic valve. All of these patients had good early and late results after the reoperation with no complications. The mean duration to reoperation was 20 ± 20 months. Late echocardiography in the remaining 69 patients revealed that 63 patients (91.3%) had up to mild AI, 4 (5.8%) had moderate recurrent AI, and 2 (2.9%) had severe recurrent AI.

Freedom from recurrent significant AI (≥ 3+) was lower in patients who underwent isolated cusp repair compared with those who underwent root or ascending aorta replacement (68% vs. 87% and 86% respectively, $P = 0.021$). Furthermore, the occurrence of the composite endpoint, recurrent severe AI or the need for reoperation was higher in patients who underwent cusp repair compared with those who underwent AV preservation without aortic cusp intervention [Figure 1A]. Between all cusp repair maneuvers, the only procedure that was correlated to failure (recurrent AI [≥ 3] or the need for reoperation), was the use of pericardial patch augmentation, as seen in univariate analysis ($P = 0.006$), and demonstrated by the Kaplan–Meier curve [Table 3, Figure 1B]. In a multivariate analysis, we also found that the use of a pericardial patch was a predictor for failure ($P = 0.048$). Other predictors for recurrent AI (≥ 3) or the need for reoperation with the aortic valve, were lower functional capacity preoperatively that was reflected by a NYHA functional class score of III–IV and a higher left ventricular end diastolic diameter preoperatively [Table 3]. While preoperative AI (≥ 3) was associated with repair failure by univariate analysis, after adjustment for confounders by multivariate analysis, it was not associated with higher repair failure.

DISCUSSION

Aortic valve pathologies in patients with BAV or UAV have an impact on quality-of-life and life expectancy and often

Figure 1. Kaplan–Meier curves for recurrent severe AI or reoperation by **[A]** AVr with or without cusp repair in the entire cohort, **[B]** with or without pericardial patch in patients who underwent cusp repair



AI = aortic insufficiency, AVr = Aortic valve repair

Table 3. Predictors for recurrent AI (≥ 3) or reoperation. A univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
AI (≥ 3)	5.8	1.57–21.06	0.008	0.8	0.11–6.25	0.860
LVEDD	3.4	1.52–7.74	0.003	3.2	1.02–9.92	0.047
Circular annuloplasty	1.4	0.41–4.42	0.615			
Cusp plication	2.4	0.65–8.65	0.190			
Pericardial patch augmentation	4.6	1.56–13.8	0.006	5.1	1.19–22.15	0.028
Subcommisural annuloplasty	2.2	0.61–8.05	0.229			
NYHA III-IV	4.2	1.12–15.94	0.034	6.1	1.12–33.12	0.036

AI = aortic insufficiency, LVEDD = left ventricular end diastolic diameter, NYHA = New York Heart Association, HR = hazard ratio, 95%CI = 95% confidence interval

require surgical intervention. The need for valve procedures in young patients raises a dilemma regarding the best approach. Generally, patients with regurgitant BAV or UAV are young when the need for valve intervention arises. While aortic valve replacement or composite aortic valve replacement (the Bentall procedure) are still the main types of procedures used, today valve repair procedures are available. One of the major considerations when treating young patients is to provide them with good quality-of-life. This result can be achieved by avoiding long-term use of anticoagulation therapy with their ensuing complications and by trying to reduce prosthesis-related complications, such as thromboembolism, bleeding, valve degeneration and endocarditis.

Our results show that AVr in patients with BAV or UAV is a safe procedure, with very good early clinical outcomes and very low morbidity and mortality rates. In our experience, long-term durability of the repair was limited for some of the patients and shorter than expected with mechanical valve implants. The limited repair durability was more pronounced when the patient needed to undergo isolated cusp repair without replacing the aorta. One reason for this result could be that when the pathology is limited to the cusps, the valve is more malformed, complicating the repair procedure. This difficulty in AVr arises from the need to maintain a delicate balance between over-tightening the valve, which could cause restricted cusps, and under-tightening, leading to regurgitation. Another reason could be that in those patients where the aorta is not replaced during valve repair, the disease of the aorta progresses over time and contributes to recurrent aortic regurgitation.

Our cohort included young patients with a mean age of 42 ± 14 years at the time of surgery. It is known that in this age group the durability of a bioprosthetic valve is not as good as in older patients. A previous report by Al-Khaja et al. [16] showed that at a mean follow-up of 7.5 years, the reoperation rate of patients younger than 40 years of age was 59%. In patients aged 40–49, the reoperation rate was 44%, while in those aged 50–59, the reoperation rate was 22%. A more recent study by Johnston and colleagues [17] showed that after 20 years of follow-up in patients younger than 60 years, the reoperation rate due to structural valve deterioration was 45% [17]. At present, when most patients with bioprosthetic valve dysfunction can undergo percutaneous valve-in-valve replacement, thereby avoiding a second open heart surgery, the age of patients who receive a bioprosthesis has decreased. However, very young patients will probably not be candidates for percutaneous valve-in-valve replacement and still many of them, under the age of 60, will require surgical reoperation. While the Ross procedure in patients with BAV is another viable option, it has been shown that in many patients with BAV who undergo the Ross procedure, there is a progression of pulmonary autograft dilatation and ascending aorta dilatation over time, thus making this procedure a less than optimal solution for these patients [18]. The present study showed that in a mean clinical follow-up of 5.8 years and echocardiographic follow-up of 4.1 years, the failure rate (severe AI or reoperation) was 16.6%. We believe that in our series the causes of failure were mostly due to problems with surgical technique and suboptimal selection criteria, both partially related to the learning curve of this type of surgery. We believe that with a better understanding of repair limitations, we will be better equipped to improve surgical solutions and upgrade patient selection, resulting in significantly improved results.

Previous publications have reported a wide range of repair durability after aortic valve sparing surgery that included aortic leaflet repair in patients with BAV. Settepani co-authors [12] reported that freedom from reoperation was 50% at 8 years, while Asano and colleagues [11] reported that freedom from reoperation was 76.6% and freedom from recurrent AI (≥ 3) was 73.4% at 5 years. Furthermore, Thudt et al. [19] reported that freedom from reoperation was 93.5% and freedom from AI (≥ 2) was 93.5% at 10 years of follow-up. A systematic review of the literature by Vohra and collaborators [20] regarding BAV repair, showed a range of 43–100% freedom from reoperation at 5 years, 49–99% freedom from reoperation at 10 years, and 71–98% freedom from recurrent AI (> 2) at 5 years. Our results lie somewhere in between. The variance of repair durability in the different series suggests the importance of experience in the various repair techniques and in patient selection. The emergence of novel technologies, such as computed tomography modeling, will be able to provide a better understanding of the BAV kinematics and geometrical characteristics of each individual patient [21]. In the future, these numerical models could assist in making the correct choice of patients who are candidates for AVr, and provide advance surgical planning. Patient-specific strategy by reconstruction of the aorta and the aortic valve could be beneficial in improving long-term results.

Currently, due to lack of consistent data, some young patients are referred for aortic valve replacement rather than AVr, even though a repair could be a superior clinical solution for them. If we would have been able to better predict which patients would benefit from a durable long-term repair, more patients could have been spared the complications associated with long-term anticoagulation therapy and other prosthesis-related complications.

Of all the maneuvers for cusp repair, we have demonstrated that the use of pericardial patch augmentation is a significant factor for failure, regardless of which other surgical maneuvers are used. Intraoperative findings and other studies suggest that the failure of the autologous pericardium is due to late calcification and shrinking of the patch over time [22]. For preparation and fixation of the pericardium many different concentrations of glutaraldehyde solutions have been proposed to reduce this late failure of the patch [23]. We used a 2% glutaraldehyde solution, which we expected would provide sufficient patch fixation with minimal cross linking of the tissue collagen. It seems that the pericardium will never provide ultimate long-term durability and therefore other materials should be explored. While no long-term results are currently available, several other materials are in clinical use, including the synthetic GOR-TEX membrane (W.L. Gore & Associates, Inc. AZ, USA), the biological CardioCel (Admedus, Malaga, Western Australia), and the CorMatrix membrane (CorMatrix Cardiovascular, Santa Cruz, CA, USA) [24,25].

In the current study, we found that a poor functional state, as demonstrated by patients with a high NYHA functional classification score (III–IV), was a predictor for repair failure. The reason for this could be related to the timing of the surgery. Had surgery been undertaken earlier, the valve could possibly have been in a more repairable state. Our results suggest that in highly symptomatic patients, it might be prudent to consider valve replacement rather than repair.

It is important to maintain the skills required to perform AVr and the ability to offer this procedure to specific groups of patients, such as those who are unable to tolerate anticoagulation therapy, as in a subgroup of young female patients who would want to give birth in the future. While AVr with a bioprosthesis is not a good solution due to its high degeneration rate in the very young, and where the Ross procedure in BAV patients has shown a progression of pulmonary autograft dilatation, AVr could provide a safe solution with good durability, especially when a pericardial patch is not needed for the repair.

STUDY LIMITATIONS

There are several significant limitations to this study. Although patients were followed prospectively, the nature of the study was retrospective. We did not find complete information on the exact anatomical features of the BAV, such as fused cusp orientation, partial fusion, and other anatomical malformations, and therefore could not conclude regarding specific anatomical risk factors for less durable repair. The clinical follow-up was longer than the echocardiographic follow-up, which could represent a problem regarding the correlation between the last echo and clinical status.

CONCLUSIONS

AVr for AI in patients with UAV or BAV, who tend to be younger when referred for surgery, is a safe procedure that provides low morbidity and mortality rates. However, improved patient selection is needed for long-term durability of the repair. In cases in which autologous pericardial patch augmentation is needed for the repair, the long-term results are less satisfactory.

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Capsule

An immune-beige adipocyte communication via nicotinic acetylcholine receptor signaling

Beige adipocytes have recently been shown to regulate energy dissipation when activated and help organisms defend against hypothermia and obesity. Prior reports indicated that beige-like adipocytes exist in adult humans and that they may present novel opportunities to curb the global epidemic in obesity and metabolic illnesses. In an effort to identify unique features of activated beige adipocytes, **Jun** et al. found that expression of the cholinergic receptor nicotinic alpha 2 subunit (*Chrna2*) was induced in subcutaneous fat during the activation of these cells and that acetylcholine-producing immune cells within this tissue regulated this signaling pathway via paracrine mechanisms. CHRNA2 functioned selectively in uncoupling protein 1-positive beige adipocytes, increasing thermogenesis through a cAMP- and protein kinase A-dependent pathway. Furthermore, this signaling via CHRNA2 was conserved and present in human subcutaneous adipocytes. Inactivation of *Chrna2* in mice compromised the cold-induced thermogenic response selectively in subcutaneous fat and exacerbated high-fat diet-induced obesity and associated metabolic disorders, indicating that even partial loss of beige fat regulation in vivo had detrimental consequences. These results reveal a beige-selective immune-adipose interaction mediated through CHRNA2 and identify a novel function of nicotinic acetylcholine receptors in energy metabolism. These findings may lead to identification of therapeutic targets to counteract human obesity.

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Eitan Israeli

"A pessimist is one who makes difficulties of his opportunities and an optimist is one who makes opportunities of his difficulties"

Harry S. Truman, (1884–1972), American statesman who served as the 33rd President of the United States (1945–1953), taking office on the death of Franklin D. Roosevelt